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NEPHRITIS

AN EXPERIMENTAL AND CRITICAL STUDY
OF ITS NATURE, CAUSE AND THE
PRINCIPLES OF ITS RELIEF

BY

DR. MARTIN H. FISCHER

Eichberg Professor of Physiology in the University of Cincinnati

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THE 1911 CARTWRIGHT PRIZE ESSAY

OF THE

ASSOCIATION OF THE ALUMNI OF THE COLLEGE OF
PHYSICIANS AND SURGEONS, MEDICAL DEPARTMENT OF COLUMBIA UNIVERSITY, NEW YORK

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TO

C. R. F.

PREFACE.

THE following pages constitute a continuation of the experimental studies in clinical physiology which were published last year under the title *Œdema*.[1] The second half of the present volume brings a detailed account of observations touched upon only incidentally there, which show how some of the severest grades of nephritis which are generally held to present considerable difficulties in treatment may be easily relieved. The methods adopted to accomplish this purpose are in no small way different from certain forms of practice common to-day. Any hope that they may find general acceptance can therefore be entertained only if the *principles* upon which the suggested therapy is based have been correctly enunciated. What to my mind these are constitutes the first half of the volume.

It is impossible to mention by name all those of my friends and colleagues who with suggestion and criticism have helped along the days' work. *Mr. Thomas Kelly* and *Dr. William H. Strietmann* have been enthusiastic and willing coworkers; *Prof. Lauder W. Jones* helped me with his store of chemical knowledge; *Mr. Alfred Brodbeck* took interest in the observations made on athletes; *Dr. Charles Goosman* gave of his time and skill to prepare the photomicrographs; *Mr. Charles Hecker* and *Mr. Peter Scherrer* of theirs to make the remaining photographs; *Mr. Paul M. Stewart* arduously deciphered the manuscript. Very sincere thanks are tendered all of them.

MARTIN H. FISCHER.

UNIVERSITY OF CINCINNATI,
June, 1911.

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[1] Œdema. A Study of the Physiology and the Pathology of Water Absorption by the Living Organism. New York, 1910. John Wiley and Sons, Publishers.

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NEPHRITIS

AN EXPERIMENTAL AND CRITICAL STUDY OF ITS NATURE, CAUSE AND THE PRINCIPLES OF ITS RELIEF.

THAT which we as clinicians have come to regard as a clinical entity, and call *nephritis*, represents in reality an aggregate of a number of conditions each of which must be treated separately if we would come to a satisfactory understanding of that which is included under the clinical term. At least silently, the necessity for such a division of the subject has, as a matter of fact, long been recognized, for have we not largely given up the discussion of nephritis and taken up more and more albuminuria, anuria, œdema, chloride retention — all of them *parts* of nephritis? Yet the persistence of the term nephritis in spite of our daily efforts in medicine to become scientifically more precise seems to be not without reason; it is the one term by which we are enabled to express the fact that the albuminuria, the anuria, etc., nearly always appear as *associated* phenomena. But from such a constancy in association we are enabled to draw an important conclusion — *they must all have a common cause.* The following pages attempt to show what this is; they try, in other words, to establish what is the underlying " cause " of nephritis.

The term nephritis is used throughout this paper in the generally accepted meaning of that word as the " non-purulent inflammations of the kidney." As will appear later, this division from the purulent forms is purely arbitrary but it is adhered to because pathologists have made this division, and it possesses certain immediate advantages for ease in discussion.

To render our argument clear, we will at once state our general conclusion:

All the changes that characterize nephritis are due to a common cause — the abnormal production or accumulation of acid in the cells of the kidney. To the action of this acid on the colloidal structures that make up the kidney are due the albuminuria, the specific morphological changes noted in the kidneys, the associated production of casts, the quantitative variations in the amount of urine secreted, the quantitative variations in the amounts of dissolved substances secreted, etc.

The proof of this contention and the discussion of how this one factor of acid production, or accumulation, in the kidney operates to produce the various changes characteristic of nephritis appears from the experimental findings that follow. We will pass at once to a seriatim analysis of the chief objective signs that as clinicians we have come to regard as characteristic of nephritis.

I. THE ALBUMINURIA.

1. Introduction.

The urine of man or of the various animals that serve us for experimental purposes does not under normal circumstances contain albumin in an amount that betrays itself when any of our ordinary laboratory tests are applied to it. By special methods it is possible to show that even such normal urine contains faint traces of albumin, but it is generally held that this is of no pathological significance and has behind it a no more serious cause (it is thought) than the shedding and destruction of a few cells from the tract through which the urine has to pass from the uriniferous tubules into the outer world. An albuminuria, as we shall use the term, will therefore have a meaning only as applied to the presence of albumin beyond this normal amount, and we ought to add of renal origin and not from somewhere below this organ. Neither are we concerned with a discussion of those albuminurias which are the consequence of the grosser destructive lesions of the kidney as in abscess. What demands an answer is the cause of those albuminurias in which no such gross lesions are apparent, where a kidney, roughly speaking, is rather normal in appearance, and still is the source maybe of large quantities of albumin.

Our current hypotheses regarding the cause of albuminuria are familiar to everyone and are notoriously unsatisfactory. It is generally held that the (chief) albumin of albuminuria is serum albumin, that it is derived from the blood, and that it is under normal circumstances prevented from going over into the urine by the kidney structures which lie between the urine and the blood. Some twenty years ago *R. Heidenhain* attempted to express the whole situation in satisfactory physicochemical terms. He pointed out the colloid nature of the blood albumins, and called to mind *Thomas Graham's* fundamental differentiation between the colloids which do not diffuse through animal membranes and the crystalloids which do this readily. On this basis he maintained that the latter appeared in the urine because they could readily diffuse through the animal membrane that separates the urine from the blood, while albumin is absent because this colloidal body cannot diffuse through such a membrane. We have not since *Heidenhain's* considerations gotten beyond this view.

Simple and apparently satisfactory as this explanation is, it cannot stand the pressure of a little analysis. In nephritis this membrane is of course still present and yet in this pathological state the albumin appears in the urine. To meet this fact it has been generally maintained, and, let us add, without any experimental support whatsoever, that the "permeability" of the urinary membrane for albumin has been altered, so that it now lets this through. As a matter of fact we have not even had offered us any parallel from the pages of physical chemistry for such a change in the permeability of any "membrane" that in the laboratory corresponds with such as we might have in the body, nor, so far as I know, has anyone attempted to say just what chemical or physicochemical agent is responsible for the changes in permeability postulated in the case of the kidney.

A first error in this theory of albuminuria (which represents the epitome of our present conceptions regarding its nature) *arises from the fact that the albumin found in the urine is looked upon as coming from the blood.* Such a belief has been entertained because it has been found that the albumin present in the urine shows a series of reactions which are identical with those obtained from serum albumin. But this does not yet prove that the albumin of albuminuria has come directly from the blood. Such a conclusion overlooks the very important fact that the albumins contained in the kidney itself, in other words the albumins contained in the secreting membrane separating the urine from the blood, also show these reactions. None of the albumin reactions used in these tests are "specific." They only represent certain group reactions which colloid chemistry has shown us to be common to a large number of the emulsion colloids of animal origin. Such considerations carry with them the important conclusion that *the albumin of albuminuria need not come from the blood at all (except* *indirectly*), *it may come from the urinary membrane itself.* That, as a matter of fact, it does come from this will appear more distinctly as we proceed. At this point let us express our conviction that *albuminuria results whenever conditions are offered in the body which permit the solid colloidal membrane that separates the blood from the urine to go into solution in the urine.* A chief reason why this occurs in nephritis resides in the fact that in this condition acids are produced which render the colloidal membrane "soluble." To make clear what is meant by this conclusion the following remarks on the general structure of the kidney, and the introduction of some observations on this question of the "solubility" of colloids are necessary.

2. The Physicochemical Structure of the Kidney.

The system that is involved in the production of urine consists in the main of three parts or phases — the blood, the urinary membrane, and the urine.

The blood consists of a liquid portion in which are floating various nucleated and non-nucleated cells. These cells are fairly solid colloid structures that in their general properties are often said to be "jellylike," a characterization that really fits them very well, for in their general biological behavior they are not unlike a stiffened gelatine, for example. But the liquid portion of the blood is also essentially colloid in character, only the colloids here are in a fluid state. It corresponds, say, with a "solution" of gelatine or of albumin or globulin. Present in both the liquid and the solid portions of the blood are normally a number of salts and various nonelectrolytes which play an important part in maintaining the normal state of the colloids that are found here. For the sake of brevity we will ordinarily in this paper refer to the whole blood as a single phase, and so as one of the phases making up the urinary secretory system. We need not especially emphasize the fact that taken strictly this is not correct; there really exist several phases within the blood itself.

Under *the urinary membrane* we will include all the structures that lie between the blood on the one side and the urine on the other. The urinary membrane as we will use the term is made up of all the different cells that are found between the blood on the one side and the urine on the other, together with their various intercellular substances. The whole constitutes a fairly firm structure to which we may again apply the term "jellylike." In the terms of physical chemistry this membrane consists of a mixture of various emulsion colloids in the solid or gel state. We find present here also, as in all the body tissues, various electrolytes and nonelectrolytes. This membrane has not the same composition everywhere. Not only does histological evidence show a striking difference in the character of the cells that make up the different parts of the urinary membrane (different cell structure in the glomeruli, convoluted and straight tubules, etc.) but so does physiological evidence (absorption of dyes). So this membrane also is itself composed of several phases, but unless specially noted we will simply refer to the whole as the second phase of our secretory system.

The third phase of our secretory system is formed by *the urine*. As is well known this is, under normal conditions, an aqueous solution of various crystalloids, — electrolytes, and nonelectrolytes. Colloidal material is present in only very small amount and consists of that trace of albumin already referred to that is found in normal urine, together with some mucin, etc., derived from the urinary tract. When the urine becomes albuminous, as in nephritis, this colloid content rises. As we have said, this is because *in albuminuria the albumin of the urinary membrane goes into* *"solution" in the urine;* the solid colloidal urinary membrane (a gel) becomes a sol. To indicate what is meant by this and to show what are the conditions that make certain solid colloids of the type that we know compose the urinary membrane go into "solution" we will detail some observations on the subject.

3. Introductory Remarks on Colloids and the Colloidal State.

As is familiar to everyone since the classical studies of *Thomas Graham* on diffusion, different chemical substances differ greatly in the rate with which they diffuse through solvents of various kinds. While such crystalline bodies as the sugars, the salts, and urea diffuse rapidly, the amorphous bodies represented by glue, starches, and various albumins do so only very slowly. While no absolutely sharp dividing line may be drawn between these two groups, the behavior of the typical members of the former is so decidedly different from the behavior of the second that there is ample justice in calling the first *crystalloids* and the second *colloids*.

Of the various substances that may be found classed under the heading colloids it is again possible to distinguish between two great groups. One of these consists of those colloids that are viscous, gelatinizing bodies which cannot be readily precipitated by salts, while another is made up of the nonviscous, nongelatinizing ones that are easily precipitated by salts (*A. A. Noyes*[1]). Typical examples of the former class are found in gelatine and various albumins, of the latter in the colloidal solutions of various metals and certain dyes. The essential difference between the two resides in the relation which the colloid bears to the solvent in which it finds itself. When these two classes of colloids are obtained in a solid form it is found that the former contains much of the solvent while the latter holds little or none. For this reason the former are also known as *lyophilic* or, if water is the solvent, *hydrophilic*, the latter as *lyophobic* or *hydrophobic* colloids (*J. Perrin*[1] and *H. Freundlich*[2]). But the terms most employed take cognizance of the fact that the separation of the solvent from the colloid is difficult to obtain in the one case because the colloid present in it is itself a liquid while this separation is easier when the colloid is a solid. For this reason the lyophilic colloids are identical with the *emulsion colloids* (or *emulsoids*), the lyophobic with the *suspension colloids* (or *suspensoids*) of *Wolfgang Ostwald.*[3]

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[1] *A. A. Noyes:* Journal of the American Chemical Society, **27**, 85 (1905).

Of these two groups of colloids our immediate problem is most concerned with the emulsion colloids, for it is of a mixture of these that the urinary membrane is composed.

The emulsion colloids are capable of existing in two fairly well defined states: in a *solid or gel state* and in a *liquid or sol state*. A familiar example of this fact is found in ordinary gelatine. Under certain conditions this appears in the form of a stiff jelly, under others as a "solution." In the same way fibrin represents the gel form of the sol fibrinogen, paracasein (casein) the gel of casein (caseinogen), ordinary soft rubber the gel of a "dissolved" rubber, etc.

It is generally recognized that in the case of the emulsion colloids a rather close relationship exists between the gel state in which the colloid is "swelled" and the sol state of this same colloid in which it is "dissolved," and yet the transition from the one state into the other is not a perfectly smooth affair. We need only call attention to the fact that ordinary gelatine, for example, when thrown into cold water merely swells up — it enters the gel state. But in this state it remains, one might almost say indefinitely; to mere appearance it does not seem to go into solution at all as would, for example, the crystals of any salt that had thus been thrown into the solvent. But if the temperature of the water is raised then the gelatine goes into solution rapidly — it passes over into the sol state. A change in temperature in this case is necessary to accomplish its "solution." As to our mind albuminuria represents just such a passage of a colloid in the gel state (the proteins of the urinary membrane) over into a colloid in the sol state (the proteins contained in the urine of the albuminuric individual), let us study the conditions favoring such a transition in a little more detail, paying especial attention to a consideration of the influence of such changes in surroundings as we might imagine could come into play in the cells of the living animal. I studied fibrin and gelatine in this regard. The following facts regarding their behavior are of importance in the further development of our subject.

---

[1] *J. Perrin:* Journal de Chimie Physique, **3**, 84 (1905).

[2] *H. Freundlich:* Kolloid Zeitschr., **3**, 80 (1908). Kapillarchemie, 309, Leipzig, 1909.

[3] *Wolfgang Ostwald:* Kolloid Zeitschr., **1**, 291 and 331 (1907). Grundriss der Kolloidchemie. Zweite Aufl. Dresden, 1911.

4. Observations on the "Solution" of Colloidal (Protein) Gels.

(*a*) *Fibrin.* — When well-washed fibrin that has been thoroughly dried and then powdered in a mortar is thrown into water it swells up somewhat. Even though the vessel is thoroughly shaken *none of the protein goes into solution in the water.* The matter is easily tested by filtering the water off the fibrin and then treating the filtrate in any of the accepted ways for albumin. One must only be careful in this simple experiment to use a fine filter or else not powder the fibrin so thoroughly that gross particles of it can pass through the pores of an ordinary paper filter. By similar means it can be shown that the *fibrin will not dis-*

solve in any solution of the ordinary neutral salts. On the other hand, if the fibrin is placed *in a solution of any acid (or alkali) it not only swells up more than in water but it goes into solution.* Within certain limits more and more fibrin goes into " solution " with every increase in the concentration of the acid (or the alkali). But in this matter there seems to exist an optimum above which the progressive increase in " solution " stops and gives way to a fall in this regard. The optimum point for the " solution " of the fibrin seems, so far as my present experiments indicate, to coincide with the optimum found for the " swelling " of this same substance. There is, moreover, an upper limit to the total amount of the fibrin that goes into solution in a given volume of the solvent. Under given conditions one has quite as much albumin in " solution " after shaking a mixture for two or three hours as after two or three days.

In a given acid or alkali mixture the amount of fibrin that will " dissolve " is markedly decreased through the addition of any neutral salt. With a progressive increase in the concentration of the salt there is a progressive decrease in the amount of the fibrin that " dissolves." But the character of the salt is not immaterial. When equimolecular solutions of different salts are compared it is found that some act more powerfully than others, but on the basis of my experiments as thus far carried out it is as yet unsafe to state definitely the order in which the various ions affect the " solution " of the solid gel. The order seems, however, to be identical with the order in which the ions affect the swelling of fibrin. Monovalent ions are, as a group, less powerful in decreasing the " solution " of fibrin in an acid or an alkali than are bivalent ions, and these than trivalent ions.

What has been said will be rendered clearer by introducing the results of a few typical experiments. Figure 1 indicates the general way in which these experiments were performed. Weighed amounts of powdered fibrin were placed in measured volumes of various solutions contained in *Erlenmeyer* flasks which were then placed in a shaking machine and shaken for various periods of time. At the expiration of this time the fibrin was allowed to settle, and the supernatant liquid was decanted off into a filter-lined funnel and received into a second flask. After stirring the filtrate, a measured volume was taken and the amount of albumin contained in it determined quantitatively through precipitation with phosphotungstic acid[1] and measurement of the heights of the precipitate either in the graduated *Esbach* albuminometer tubes or ordinary test tubes of uniform diameter. As the experiments are purely comparative in character I have contented myself in this paper with simply photographing the results of a few of such experiments as have a direct bearing upon our subject.

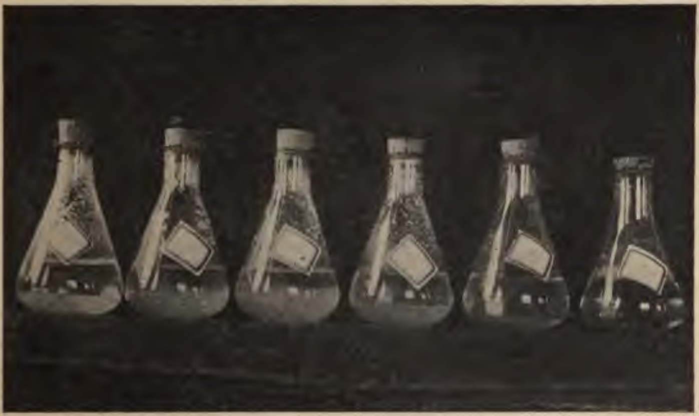

FIG. 1.

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[1] The phosphotungstic acid reagent had the following composition:
Phosphotungstic acid, 100 grams.
Sulphuric acid (sp. gr. 1.84), 100 grams.
Water enough to make 1000 c.c.

EXPERIMENT 1. — 0.5 gram of powdered fibrin was shaken up for 5 hours in each of the following solutions:

1. 50 c.c. 0.008 normal HCl.
2. 50 c.c. 0.012 normal HCl.
3. 50 c.c. 0.02 normal HCl.
4. 50 c.c. 0.04 normal HCl.
5. 50 c.c. 0.1 normal HCl.
6. 50 c.c. H_2O.

The appearance of the fibrin in each of the flasks at the end of this time is shown in Fig. 1. In the first three flasks (1, 2, 3) there is a progressive increase in the *swelling* of the fibrin with the progressive increase in the concentration of the acid. Beyond this point (flasks 4 and 5) there is a decrease in the swelling in spite of the further increase in the concentration of the acid. The least amount of swelling is noted in flask 6 which contains water only. The *solution* of the fibrin is indicated in Fig. 2. From left to right these tubes correspond with the flasks of Fig. 1. No precipitate of albumin is seen in the tube on the extreme right, indicating that the fibrin did

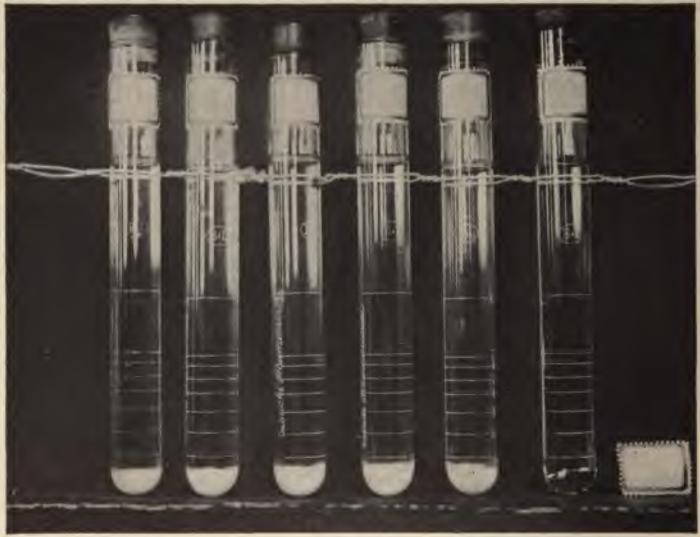

FIG. 2.

not go into solution in the water (neutral reaction). All the remaining tubes show a precipitate of albumin.

EXPERIMENT 2. — 0.5 gram of powdered fibrin is put into each of the following solutions and shaken for 5 hours:

1. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. H_2O.
2. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{8}$ molecular NaCl.
3. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{6}$ molecular NaCl.
4. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{4}$ molecular NaCl.
5. 50 c.c. H_2O.

The amount of albumin that went into solution is indicated in Fig. 3. No precipitate is seen in the tube on the extreme right (water). Most albumin is found in the first tube (pure acid solution). It is evident that the presence of the sodium chloride reduces the amount of the albumin that goes into solution. The amount of this reduction is the greater the higher the concentration of the salt.

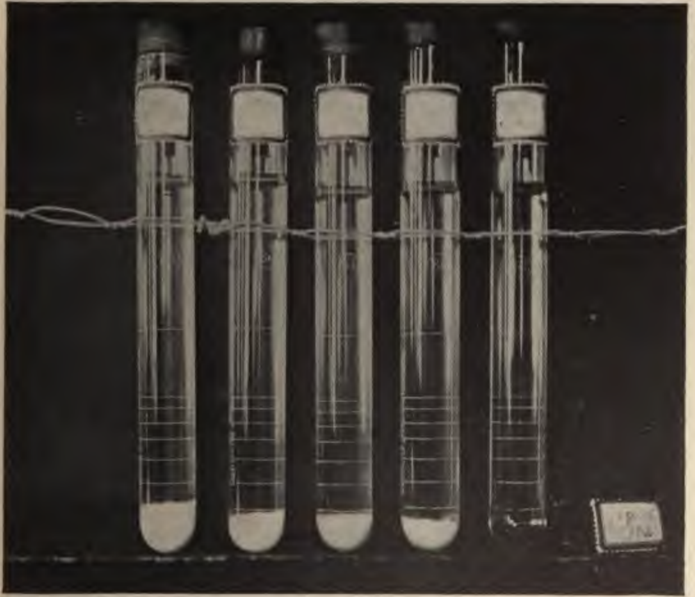

FIG. 3.

EXPERIMENT 3.—0.5 gram of powdered fibrin was placed in each of four flasks containing the following solutions and shaken for 5 hours:

1. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. H_2O.
2. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{8}$ molecular Na_2SO_4.
3. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{8}$ molecular $MgSO_4$.
4. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{8}$ molecular $CuSO_4$.

After filtering, the amount of albumin dissolved in the supernatant liquid found above the fibrin in each of the flasks was determined by mixing 20 c.c. of filtrate with 14 c.c. phosphotungstic acid. The result is shown in Fig. 4. As is readily apparent, each of the salts markedly reduced the amount of albumin that was dissolved.

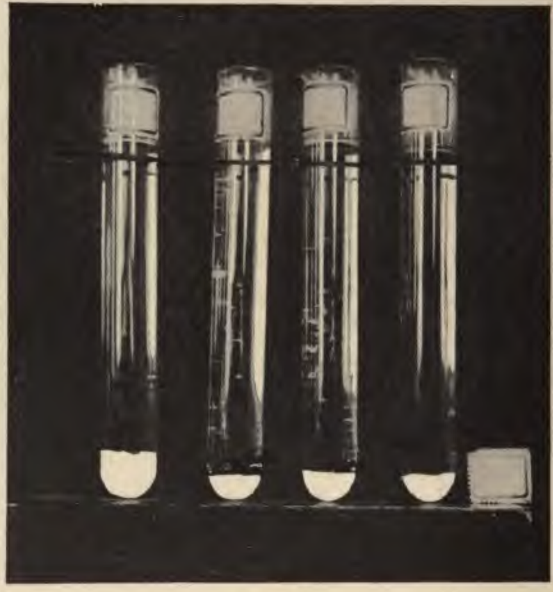

FIG. 4.

EXPERIMENT 4. — 0.5 gram of powdered fibrin was introduced into each of five flasks containing the following solutions and shaken for 5 hours:

1. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{8}$ molecular sodium acetate.
2. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{8}$ molecular sodium nitrate.
3. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{8}$ molecular sodium sulphate.
4. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. $\frac{1}{8}$ molecular sodium citrate.
5. 10 c.c. $\frac{1}{10}$ normal HCl + 40 c.c. H_2O.

The relative amounts of albumin found dissolved in each of these mixtures at the end of this time are indicated in Fig. 5. As is again evident, most albumin was dissolved by the pure acid solution. Each of the salts decreased through its presence the amount thus dissolved.

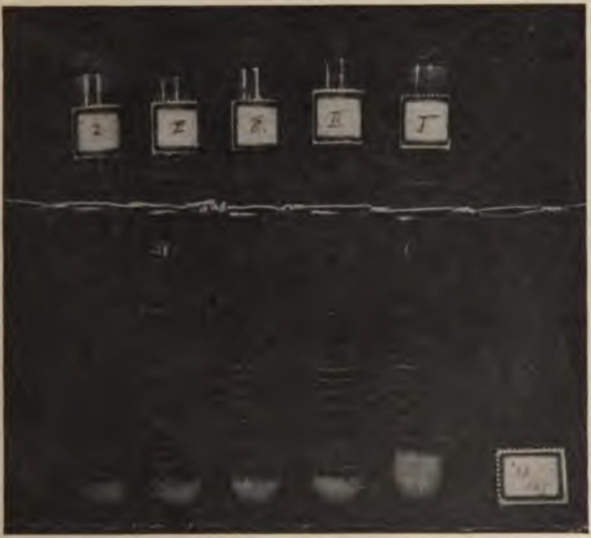

FIG. 5.

(*b*) *Gelatine. — What has been said under paragraph* (*a*) *regarding the "solution" of fibrin holds almost word for word for the "solution" of gelatine.* The best commercial gelatine shows some solubility in water. The commercial product, as is well known, has a decidedly acid reaction. When, instead of being placed in water, gelatine is dropped into solutions of acids (or alkalies) this solubility of the (commercial) gelatine is greatly increased. The presence of neutral salts in the acid (or alkali) solution decreases the amount of the gelatine that will go into solution. As in the case of fibrin we note here again a progressive decrease in the amount that "dissolves" with every increase in the concentration of the added salt. With a given concentration, the amount of such a decrease varies with the salt employed, and here again it seems that monovalent ions do not as a group decrease the "solubility" of the gelatine as much as bivalent ions, or these as much as trivalent ions.

The following experiments will serve in illustration of what has been said.

EXPERIMENT 5. — The following solutions were prepared:

1. 100 c.c. H_2O.
2. 100 c.c. 0.001 normal HCl.
3. 100 c.c. 0.002 normal HCl.
4. 100 c.c. 0.005 normal HCl.
5. 100 c.c. 0.01 normal HCl.
6. 100 c.c. 0.015 normal HCl.
7. 100 c.c. 0.02 normal HCl.
8. 100 c.c. 0.025 normal HCl.
9. 100 c.c. 0.035 normal HCl.

Five leaves of dry gelatine, each measuring 3½ by 1½ cm., weighing altogether 0.5 gram, and obtained by cutting them out of the central portions of the large gelatine leaves that are obtained commercially, were dropped into each of these solutions. From time to time the dishes containing the solutions with their gelatine leaves were agitated so as to keep the gelatine from adhering to the sides, and aid the solution of the gelatine. All the vessels were treated exactly alike. The degree of solution of the gelatine after 28 hours in these various solutions is indicated in Fig. 6. As the photograph shows, least gelatine is dissolved in the pure water. With the increase in the concentration of the acid there is a progressive increase in the amount of dissolved gelatine, but only up to a certain point, after which it falls in spite of the continued further increase in the concentration of the acid.

EXPERIMENT 6. — In the manner just described, 5 leaves of dry gelatine, weighing in toto 0.5 gram, and of the same surface were placed in each of the following solutions:

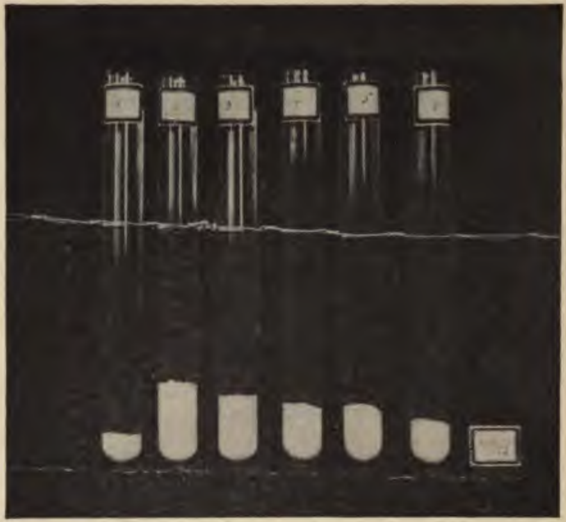

FIG. 7.

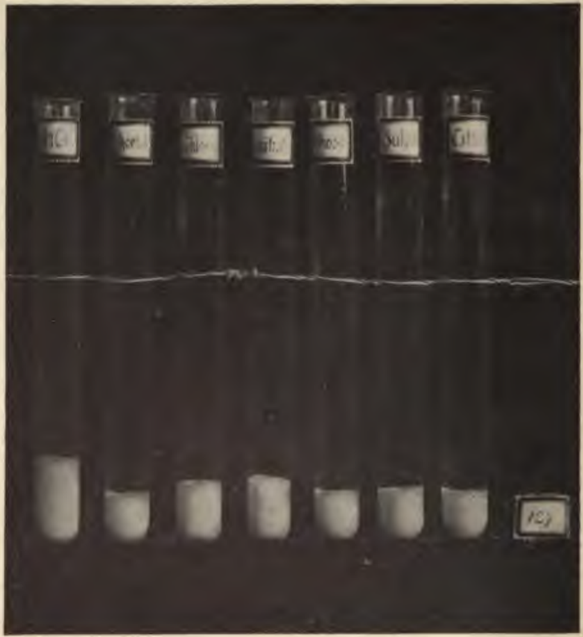

FIG. 8.

6. 15 c.c. $\frac{1}{10}$ n. HCl + 40 c.c. $\frac{1}{2}$ mol. sodium sulphate + 45 c.c. H_2O.
7. 15 c.c. $\frac{1}{10}$ n. HCl + 10 c.c. $\frac{1}{1}$ mol. sodium citrate + 75 c.c. H_2O.

The relative amounts of gelatine dissolved in these various solutions after the gelatine leaves had with occasional agitation remained in them for 19½ hours are indicated in Fig. 8. As is readily evident, each of the salts decreases by its presence the amount of gelatine dissolved in the acid solution. The divalent and trivalent anions are more powerful in this respect than the monovalent ions, with the exception of the acetate. The intermediate position taken by this ion, in this matter of the solution of the gelatine, corresponds with the intermediate position occupied by this same ion in the swelling of the colloid under similar circumstances.

It is clearly apparent from what has been said that the "solution" of two typical emulsion colloids (protein gels) is intimately connected with the character of the medium in which these gels find themselves. Acids (and alkalies) favor their solution while various other substances (notably salts) either do not affect the solubility of the gel at all, or if present in conjunction with an acid (or alkali) depress the amount that would have been "dissolved" if the acid (or alkali) had been present alone.

We will now adduce the evidence which is intended to show that *the colloidal gel that constitutes the urinary membrane goes into "solution" in the urine (albuminuria results) under the same conditions under which fibrin or gelatine gels go into "solution" in water.*

5. Albuminuria as a Phenomenon Identical with the "Solution" of a Protein Gel.

No special argument is necessary to prove that *what lies between the urine on the one hand and the blood on the other (the kidney) represents physicochemically a colloidal gel.* The general physical properties of the kidney as a whole betray this fact, and from chemical analysis we know that the albumins, globulins, higher carbohydrates, fats, and

" lipoids " which constitute, exclusive of water, the bulk of this organ, are all to be counted in the group of our most typical emulsion colloids. What we need to show is that under normal circumstances, in " health," the conditions are such as to keep these colloids (as we are discussing albuminuria this means the proteins) in the gel state, while under other circumstances (for example in nephritis) conditions are offered which permit these colloids to pass over into the sol state and so escape with the urine. As we found changes in the reaction of the medium to play a most important rôle in the " solution " of such emulsion colloid gels (fibrin and gelatine), we will direct our chief inquiry into the question of whether such changes occur in the kidney in every condition characterized by an albuminuria. *An abnormal production or accumulation of acid in the kidney lies at the bottom of every albuminuria and is responsible for it.* Our support for such a view will come from three directions.

1. Evidence of an abnormal production or accumulation of acid in the kidney, or conditions predisposing thereto, exist in every case of albuminuria, and conversely;
2. Any means which leads to an increased production or favors the accumulation of acid in the kidney results in albuminuria.
3. Any means by which we can decrease the " solubility " of various protein gels (fibrin and gelatine) in an acid medium constitutes a means by which we can decrease albuminuria.

The first two of these we will consider at once. The third we will take up separately later in this paper when we discuss the subject of the treatment of nephritis.

§ 1.

1. If albuminuria is to be regarded as a process of "solution" of the urinary membrane in consequence of the presence of acids in it, then evidently the maintenance of the gel state of the normal membrane must be intimately associated with a maintenance of *neutrality* in it. We are therefore first of all interested in the fact that (exclusive of the gastric juice, the urine, and less positively, the sweat, vaginal secretion, and alimentary contents when fat is fed) *the fluids and tissues composing the living mammal are to all intents and purposes neutral in reaction and are capable of maintaining this neutrality against the introduction of considerable acid into them.*

In the terms of our modern physical chemistry, an acid reaction is due to the presence of free hydrogen ions, an alkaline reaction to the presence of free hydroxyl ions. A neutral reaction means, therefore, one of two things: either neither of these ions are present, or else just as many of the one as of the other, so that they balance each other (the latter is the case in the body). The neutral reaction of the blood (and from this it has been generally assumed that the tissues themselves are also neutral in reaction) seems at first sight a rather surprising fact when considered in the light of our older teachings that the body fluids and the cells are all "alkaline." But these older teachings are erroneous for they are based upon an improper interpretation of the results obtained with titration methods. The blood, for example, has generally been held to be "alkaline" because it is capable of neutralizing acid. But as we know now, the power of a solution to neutralize an acid is no index of its content of free, that is to say, active, hydroxyl ions which is the true measure of its alkalinity. For a proper measure of this hydroxyl ion concentration in the blood (or in the tissues) all the determinations are valueless that antedate the fundamental measurements of *P. Fraenkel*,[1] *G. Farkas*,[2] and *Rudolf Höber*[3] who first used proper physico-chemical methods (so-called gas chains) in the biological study of this problem. The observations of all these authors agree in *pronouncing the normal blood neutral in reaction*; *as neutral as pure distilled water.*

Of further interest is the fact that *this state of neutrality of the blood* (*and of the tissues*) *is maintained against the introduction of considerable acid or alkali into them.* When exposed to the action of an acid, it is found that the normal hydroxyl ion concentration of the blood drops with the progressive introduction of acid into it in the form of a curve, which falls only very slowly at first, and then more rapidly. Just why and how the state of neutrality is thus maintained for a period does not at this particular moment interest us, but it may not be amiss to point out that two factors are involved in the process. The first lies in the fact that such salts as sodium carbonate and disodium hydrogen phosphate are capable of uniting with acids (carbonic and phosphoric acids) to form salts having a higher hydrogen content (sodium bicarbonate and sodium dihydrogen phosphate), but which in their dissociation yield few more *hydrogen ions* than the salts from which they were originally formed and which were present in the blood to start with. In other words, there is for a time only a slight increase in the concentration of the hydrogen ions (increase in acidity) in spite of the considerable introduction of free acid into the system. (*L. J. Henderson.*)[4]

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[1] *P. Fraenkel:* Pflüger's Archiv, **96,** 601 (1903).

[2] *G. Farkas:* Pflüger's Archiv, **98,** 551 (1903); Archiv f. (Anat. und) Physiol., Supplement, 517 (1903).

[3] *Rudolf Höber:* Pflüger's Archiv, **81,** 522 (1900); **99,** 572 (1903).

[4] *L. J. Henderson:* American Journal of Physiology, **15,** 257 (1906); **21,** 169 (1908); **21,** 427 (1908); Ergebnisse d. Physiologie, **8,** 257 (1909), where extensive references to the literature will be found.

The other and lesser element for the maintenance of neutrality resides in the amphoteric character (that is to say their power of combining either with acids or alkalies) of the colloids found in the blood or the tissues. The albumins, for example, can unite with considerable quantities of acid (or alkali) without any decided change in their behavior toward indicators. The presence of certain colloids in any system will therefore serve to delay the increase in the concentration of the hydrogen ions when an acid is added to this system.[1] But let not the impression be gained from these remarks that the blood or the tissues are not sensitive to even very minute additions of acid (or alkali) to them. Such an increase in the concentration of the carbonic acid as occurs when normal arterial blood becomes venous is already sufficient to reduce the hydroxyl ion concentration in the latter to one half that existing in normal arterial blood. How profoundly even such a change affects the state of the colloids we will have occasion to discuss later. For the present we are content with making the point that *the blood and (presumably) the tissues are neutral in reaction, that they are capable of maintaining this neutrality within rather wide limits, even when subjected to the action of an acid, and that in consequence, under normal circumstances, conditions are such in the cells of the kidney as to maintain the colloids here in their gel state.*

2. As modern physicochemical studies have reduced what we formerly regarded as the "alkalinity" of the blood to a point where we may call it neutral, so also have they reduced the normal "acidity" of the urine from what we used to assume this to be. Just as the neutralizing power

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[1] *J. Sjöqvist:* Skand. Arch. f. Physiol., **5**, 277 (1895); *Otto Cohnheim:* Zeitschr. f. Biol., **33**, 489 (1896); *K. Spiro* and *W. Pemsel:* Zeitschr. f. Physiol. Chem., **26**, 233 (1898), *S. Bugarszky* and *L. Liebermann:* Pflüger's Arch., **72**, 51 (1898); *T. B. Robertson:* Jour. of Physical Chem., **11**, 542 (1907); **12**, 473 (1908).

of the blood for acids is no indication of its true reaction, so also is the amount of alkali with which a given specimen of urine will combine no measure of its true, that is to say, active, acidity. To gauge this properly the concentration of the hydrogen ions in it must be determined and this was not done until *von Rhorer* [1] and *Rudolf Höber* [2] applied the principle of the gas chain to the physicochemical analysis of the urine. The following Table I, taken from *Höber*,[3] indicates what is the concentration of the hydrogen ions in a series of *normal* morning urines. This gives a measure of their true acidity.

TABLE I.—NORMAL URINE.

Hydrogen ion acidity ($10^{-5} \cdot C_H$).	Titration acidity.
0.58	0.046
0.52	0.034
0.50	0.042
0.46	0.069
0.31	0.075

It would support our idea of the cause of albuminuria if it could be shown that *this acidity of the urine increases in conditions associated with an albuminuria.* How strikingly true this is, is clearly evident from the following analyses of *nephritic* urines also taken from *Höber* and made of course without thought of using them for such purposes as we do here.

As is clearly evident on comparing these two tables the active acidity of the urine of nephritics may be more than four times that of the normal urine. But Table II already suffices to betray another fact. *The highest acidities occur*

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[1] *L. von Rhorer:* Pflüger's Archiv, **86,** 586 (1901).

[2] *Rudolf Höber:* Hofmeister's Beiträge, **3,** 525 (1903).

[3] *Rudolf Höber:* Physikalische Chemie d. Zelle u. d. Gewebe. Zweite Aufl. 158. Leipzig, 1906.

in the acute forms of nephritis, in other words, in the same forms in which we find most albumin. The lowest values are found in the chronic interstitial forms, in other words, in the very types in which albumin is very likely to be found only in traces or at times not at all. The degree of the albuminuria therefore follows very closely the degree of acidity. We shall have occasion to return to this question later.

TABLE II. — ABNORMAL URINE.

Hydrogen ion acidity ($10^{-5} \cdot C_H$).	Titration acidity.	Remarks.
2.34	0.019	Interstitial nephritis.
1.50	0.018	
0.84	0.027	
1.10	0.020	
2.20	0.022	Acute nephritis.
2.10	0.020	
0.56	0.014	Chronic interstitial nephritis.
0.67	0.050	

Let us now look at the columns in these tables that record the *titration* acidities. It is such values — erroneously interpreted as measures of the true acidity of the urine — that we find recorded in all the studies of nephritis. When the individual titration acidities in the above tables are compared with their corresponding active acidities as determined by measuring the hydrogen ion concentrations in the urine, it is readily apparent that the two values do not even approximately parallel each other. What is learned when the titration acidity of the urine is determined is its ***capacity to neutralize alkali. Under otherwise constant conditions*** it is clear that this titration acidity of the urine must grow with every increase in the amount of acid in the urine. ***The uniformly higher titration acidity of the urine in nephritis,*** as is shown not only in the above tables I and II but by the scores that may be found in any of the larger works that deal with this question of nephritis, *becomes further evidence therefore in favor of our contention that an abnormal production or an abnormal accumulation of acid occurs in the kidney in every albuminuria.*

3. In the same way that we use the increased alkali capacity of the urine as evidence for the presence of abnormally large amounts of acid in it (and so in the kidney cells from which this comes), so also may we use the decreased acid capacity of the blood as evidence in the same direction. The titration values of the blood, which the older clinical observers looked upon as indices of its "alkalinity," may be drawn upon for evidence to show that in the albuminurias there exists a decreased power of the blood to neutralize acids. As studied particularly by *Rudolf von Jaksch,*[1] *W. H. Rumpf,*[2] *E. Peiper*[3] and *F. Kraus*[4] *a decrease in the acid capacity of the blood is noted in no conditions more strikingly than in nephritis and its oft associated uræmia.*

4. Our argument thus far has shown that in nephritis there is a great increase in the true acidity of the urine, and that in both the urine and the blood there occur changes in the titration values which clearly indicate that both are holding a more than normal amount of acid. Our knowledge of physical chemistry (the laws of chemical equilibrium) permits us to utilize these facts as evidence indicating that the *tissues* of the kidney which lie between the urine on the one hand and the blood on the other (all that we in our definition sum up as the urinary membrane) must, under such circumstances, also show a rise in acid concentration. But it would further strengthen this view if we could bring a more direct proof in support of this de-

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[1] *R. v. Jaksch:* Zeitschr. f. klin. Medicin, **13**, 350 (1887).

[2] *W. H. Rumpf:* Centralbl. f. klin. Medicin, **12**, 441 (1881).

[3] *E. Peiper:* Virchow's Arch., **116**, 337 (1889).

[4] *F. Kraus:* Zeitschr. f. Heilkunde, **10**, 106 (1889); Archiv f. exp. Path. u. Pharm., **26**, 181 (1889).

duction. It would be well of course if we could obtain a direct measure of the hydrogen ion concentration in the kidney. Gas-chain methods are naturally not applicable to solid organs, and to apply them to the expressed juice of the kidney would be to introduce so many errors into the whole problem as to render the conclusions valueless. We can, however, obtain material help by using indicators.

Proof of an increase in the amount of acid held by the kidney cells in conditions associated with an albuminuria is furnished by the following facts:

In 1885, *H. Dreser*[1] described a series of experiments on the excretion of dyes by the kidney which differed from the preceding studies of this subject as first made by *R. Heidenhain*[2] and *M. Nussbaum,*[3] in that he utilized the results of his experiments in an attempt to get an answer to the question as to where in the kidney the acid of the urine is secreted. *Dreser* made chief use of acid fuchsin which he injected in 5 to 10 per cent solutions (amounts not stated) into the dorsal lymph sacs of frogs. This dye has the property of being red in aqueous solution only in the presence of an acid; in an alkaline solution it becomes practically colorless (yellow). *Dreser* therefore reasoned that the presence of a red color in any tissue after the injection of this dye into the circulation of an animal was evidence for an acid reaction in that tissue. The first fact noted by *Dreser* that is of interest to us is that after a single dose of acid fuchsin the urine is found shortly thereafter to become brilliantly red. If the kidney from such an animal is examined no stained cells are noted anywhere in the kidney. To interpret this fact we would have to say that normally *the urine is acid in reaction but the cells of the*

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[1] *H. Dreser:* Zeitschr. f. Biol., **21,** 41 (1885); *ibid,* **22,** 56 (1886).

[2] *R. Heidenhain:* Pflüger's Archiv, **9,** 1 (1875).

[3] *M. Nussbaum:* Pflüger's Archiv, **16,** 141 (1878).

normal kidney have not an acid reaction. The following may serve to corroborate this finding of *Dreser.*

Experiment 8. — Three frogs, weighing 35 grams each, are injected, respectively, with 0.25, 0.5, and 1.0 c.c. of an aqueous 1 per cent acid fuchsin solution, into the dorsal lymph sac. All are seen to secrete a red colored urine before being killed. They are killed respectively after 1, 1½, and 4½ hours. On autopsy, *red urine is found in the bladder of each animal. The kidneys are not stained.* They are rapidly removed from the freshly killed animals, frozen with liquid carbon dioxide gas (on a *Bardeen* freezing microtome where the gas does not come in contact with the tissue) and sectioned. The sections are immediately transferred to a slide (without being brought in contact with water or any other medium except air), covered with a cover slip, and examined under the microscope. *None of the kidney tissues are seen to be stained.* To be sure that the freezing plays no part in the findings, a parallel series of free-hand sections, and crush preparations of the kidneys are made. No stained cells are found.

When the uncolored sections are touched with very dilute acetic acid they are seen gradually to assume a pink color. *Acid fuchsin is therefore present in the kidney tissues,* but as cut from the body the reaction of this organ is not such as to allow its red color to appear. The pink tinge visible in the kidney after being touched with acid *includes the glomeruli.*

Experiment 9. — To show that what was said for the frog holds also for the mammal, two young rabbits, weighing, respectively, 184 and 189 grams, received into the ear veins 2.0 and 4.0 c.c., respectively, of a 1 per cent aqueous acid fuchsin solution. At the end of 30 and 35 minutes, respectively, they were killed by a blow on the head and immediately autopsied. Light red urine was found in the bladder of the first, deep red urine in that of the second. The appearance of the kidneys in both animals was entirely normal, and no dye was visible in the kidneys either macroscopically or microscopically. When a little very dilute acetic acid was permitted to flow under the cover slips, the sections turned uniformly pink.

Dreser noted no staining of the frog's kidney until he had repeated his acid fuchsin injections several times. Then he found that the cells of the convoluted and of the straight tubules began to stain red. He interpreted this finding by saying that from the long-continued effort on the part of these cells to excrete the dye, they become fatigued and so some of the dye remains behind to be discovered on subsequent section of the kidney. From all these facts *Dreser* concluded that the acid constituents of the normal urine are "secreted" by the convoluted tubules, and that since the glomeruli and their capsules remain unstained, the "urine" coming from these must be "alkaline" in reaction, to change to an acid reaction after passing by the convoluted tubules. Whether such conclusions are really justified we shall have occasion to discuss later.

No one can quarrel with the simple experimental finding that acid fuchsin does not stain the normal kidney, and does do this after repeated and long-continued injections. Such staining of the kidney *Dreser* still regards as "physiological." Strictly speaking, and for reasons that will be apparent as we go on, I should myself be more inclined to regard it as "pathological." What *Dreser* calls *the "fatigue" of the cells of those portions of the kidney which stain after repeated injections of the acid fuchsin, we are perfectly safe in regarding as the first evidences of an abnormal acid content in these cells, and we may hold that the repeated injection of this dye is itself responsible for such a condition.*

Acid fuchsin is a weak acid, and must produce the same effects upon the kidney that we know are produced by the injection of any other acid.[1] After the injection of acids we note regularly all the signs of a nephritis, and that these were not absent in *Dreser's* experiments is clearly evidenced by the "anuria" which this author so often noted in his frogs.

But *Dreser*[2] describes yet another experiment which shows that an abnormal production or storage of acid occurs in the kidney in nephritis. The kidney of the frog receives a blood supply, it will be remembered, from two sources — through the renal artery, as in mammals, and through a sort of portal system analogous to that existing in the liver. The blood from both these sources mixes to leave the kidney by way of the renal vein. *Dreser noted that if acid fuchsin is injected into the abdominal vein an hour after the renal artery has been tied, the convoluted tubules stain red.* As already pointed out, no such red staining of the cells is noted if the dye is so injected without ligature of the renal artery. *Dreser* interprets his finding in terms of physiology, but that we deal here with a pathological condition of the kidney — a nephritis — is evidenced not only by the fact noted by *Dreser*, that kidneys so treated secrete no urine, but by the evidence furnished below,[1] that after occlusion of the arterial blood supply to the kidney, acid develops in this organ, the kidney swells, the water secretion falls, and casts and albumin appear in the urine.

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[1] See the succeeding § 2 on page 35.

[2] *H. Dreser*, Zeitschr. f. Biol., **21**, 53 (1885).

Further tinctorial evidence of an abnormal production or accumulation of acid in the kidney in nephritis is furnished by certain experiments of *R. Heidenhain*, *M. Nussbaum*, and *P. Grützner* with sodium indigosulphonate. This dye behaves in a way entirely similar to that of acid fuchsin. It is deep blue or indigo in an acid solution and yellow in an alkaline solution. The somewhat contradictory conclusions of these authors, based on their studies with this dye, are easily put in order if we try to separate those of their findings which are pathological from those which are physiological. In my own experiments on rabbits and frogs, I have, first of all, never been able to confirm any but the conclusion of *Nussbaum*[2] that *no part of the normal*

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[1] See pages 50, 123 and 151.

[2] *M. Nussbaum:* Pflüger's Archiv, **16**, 141 (1878).

kidney stains with sodium indigosulphonate. This corroborates the finding obtained with acid fuchsin — *the normal kidney is not acid in reaction.*

EXPERIMENT 10. — Four frogs, weighing 30 grams each, are injected, respectively, with 0.25, 0.5, 1.0, and 0.25 c.c. of a 1 per cent aqueous sodium indigosulphonate solution into the dorsal lymph sac. Blue urine is voided by each of the animals before being killed. After, respectively, 40 minutes, 50 minutes, 70 minutes, and 3½ hours, their heads are cut off and they are autopsied. Blue urine is found in the bladders of the last three. Macroscopic examination shows *no color anywhere in the kidneys of these animals*, and microscopic examination of frozen sections only confirms this fact.

EXPERIMENT 11. — Three rabbits from the same litter, and weighing 497, 575, and 447 grams, respectively, receive, respectively, through the ear vein, 1, 2, and 5 c.c. of a 1 per cent aqueous sodium indigosulphonate solution. They are killed by a blow on the head one hour after being injected. Blue urine is found in the bladder of each. This is also present in the ureter of the third. *The kidneys are entirely unstained* in the first two, and no color is found anywhere in the frozen sections prepared from these kidneys. The kidney of the third animal has a mottled blue appearance superficially, and one section shows some blue streaks radiating toward the pelvis of the kidney. *Frozen sections show no dye anywhere in the kidney substance proper.* The blue streaks are due to dye found in the *lumina* of a few of the collecting tubules.

In apparent contradiction to this simple conclusion that the normal kidney does not stain with sodium indigosulphonate, stand the classical experiments of *Heidenhain*,[1] who found certain portions of the kidney, notably, again, the convoluted tubules, to stain when the "secretion of the urine was sufficiently depressed." *Heidenhain* brought about the desired reduction in the secretion of urine by such procedures as transverse section of the spinal cord in the neck. But as he himself has noted, this produces an enormous fall in blood pressure. Such a fall in blood pressure does not, however, leave the kidney in a normal condition — it spells not alone an anuria but an albuminuria, and casts, in other words, a "nephritis." *The staining of the kidney under these circumstances is again evidence of an abnormal production or accumulation of acid in this organ*, a conclusion that we shall shortly be able to corroborate by entirely different methods.

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[1] *R. Heidenhain:* Pflüger's Archiv, **9**, 1 (1875); Hermann's Handbuch d. Physiol., **5**, 346. Leipzig, 1883.

Both *Heidenhain* and *Dreser* have laid special stress on the fact that the convoluted tubules stain under the conditions offered in their experiments, while the glomeruli remain unstained, because it is upon this fact chiefly that they (and their followers) have based their conclusion that the different parts of the uriniferous tubule in its course from the glomerulus to the pelvis of the kidney have different functions. As generally held, these different parts are supposed to secrete into (or, according to *Carl Ludwig*, absorb from) the mother urine, — the liquor postulated by *W. Bowman* to be separated from the blood in its passage through the glomeruli, — as this flows down the uriniferous tubules, the different substances which serve to characterize the urine. Now, I do not myself question the probability that the different portions of the uriniferous tubules have different functions, but strictly speaking, this is not proved by these particular experiments. The findings of *Dreser* and *Heidenhain* show only that, *under the conditions of their experiments, the neutrality mechanism existing in the convoluted tubules is broken down more easily than that existing, for example, in the glomeruli.* That this approximates more nearly a correct interpretation of the observed phenomena is, as a matter of fact, indicated by the following:

By simply continuing the conditions which were mentioned as effective in leading to a staining of the convoluted tubules, we get a staining of the glomeruli. Evidence for the correctness of this conclusion can be adduced even from some cursory experiments mentioned by *Heidenhain* and *Grützner*. As pointed out above, the conditions which lead to a staining of certain portions of the kidney with acid fuchsin or sodium indigosulphonate (excessive acid injection, ligature of renal artery, gross falls in blood pressure) are conditions which we can show by other means to be such as are associated with an abnormal production or accumulation of acid in the kidney. No matter how we interfere with a proper blood supply to the kidney we get such a production of acid. It does not therefore surprise us to note that when *P. Grützner*[1] produced circulatory disturbances in the kidney by injecting gum arabic, he noted not only the development of anuria and albuminuria, but he found at the same time that the glomeruli and their capsules now stained with sodium indigosulphonate. Quite as simply can we interpret *Heidenhain's*[2] finding that the glomerular tufts stain with sodium indigosulphonate when the ureters are ligated. When this is done the urine is dammed back and accumulates in the space between the glomerular tuft and the parietal layer of the capsule, in consequence of which the capillaries composing the tuft are compressed, so that the normal circulation of blood cannot now occur through them. Under these circumstances an abnormal production or accumulation of acid in the cells of the glomerulus and the capsule is rendered possible and so the tissues making up these structures now stain.

One can further test the soundness of the reasoning detailed here, namely, that a staining of the kidney as a whole or in part marks the presence of an acid, by working with excised kidney. Slices of fresh kidney kept in dilute solutions of sodium indigosulphonate or acid fuchsin stain only very slowly and very slightly. Hours elapse before even a faint tinging of the tissues of the kidneys results. But let a trace of acid be added and *all* parts of the section may be made to stain a deep blue in a few minutes. In the same way a section of tissue from a kidney that has been dead some time (and so contains post mortem acids) stains readily, and, let it be noted, in all its parts.

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[1] *P. Grützner:* Pflüger's Archiv, **24**, 461, 1882.

[2] *R. Heidenhain:* Hermann's Handbuch d. Physiol., **5**, 372. Leipzig, 1883.

It will be recalled by anyone familiar with such studies as those of *Heidenhain*, *Dreser*, or the numerous investigators who since their day have adopted similar experimental methods, that these studies are intended to throw light on the problem of secretion by the kidney cells. This process of secretion is, of course, made up of two parts, the one concerned with the taking up from the blood of the substance to be secreted, the other with the giving off of this same substance in the urine. The problems involved here are discussed in detail later, but it may not be amiss to point out even now that what is so often done, namely, the regarding of a mere staining of some or all of the cells of an organ as dependable evidence indicating that the dye is " secreted " by these cells, is entirely wrong. The presence of a dye in a cell does not mean this; nor when cells stain unequally does it mean that those most deeply stained are most involved in this process. *It may mean just the reverse.* The staining of the excised kidneys described above shows this very clearly. A kidney touched with a little acid, or one showing post mortem change, stains better than a normal kidney, and this without any hope of subsequently "secreting" the absorbed dye. Again, a kidney rendered "nephritic" by ligation of its arterial blood supply stains better than a normal one, and yet no one would maintain that a nephritic kidney "secretes" all dissolved substances better than a healthy one.

What really happens in the excised kidneys, or in the "nephritic" kidneys contained in the still living animal, represents but an isolated expression of the general laws that we to-day know to underlie all that is comprised in the physical chemistry of the dyestuffs. *The kidney cells in the experiments that have been detailed are stained for the same reason, and their staining reactions mean the same thing, as when any ordinary lyophilic colloid such as fibrin or gelatine takes up acid fuchsin or sodium indigosulphonate.* If these colloids are seen to be stained red or blue it means, first of all, that they have, under the conditions of our experiment, an acid reaction. But with a given concentration of the dye the depth of the staining becomes a measure of the degree of such an acid reaction, for a given colloid will absorb the more of any so-called "acid stain" the higher the concentration of the acid in which it finds itself. Other things being equal, the kidney cells must stain the more intensely with acid fuchsin or sodium indigosulphonate, the higher the acid concentration developed in them. To this whole question we shall have to return later.

§ 2.

We are now ready to discuss the converse of what has gone before, and so try to show that *any means by which we can bring about an abnormal production or accumulation of acid in the kidney constitutes a method of producing an albuminuria.*

1. The simplest way to upset the normal conditions of neutrality as existing in the kidney lies, of course, in the *introduction into this organ of an acid* of some kind. This is done most easily by injecting the acid, either in solution in water or in a "physiological" salt solution, directly into the general circulation of an animal. For this purpose I used, in my own experiments, a large-sized aspirating syringe

with a two-way valve, rubber tubing, and a hypodermic needle, as illustrated in Fig. 9. The acid solution warmed to 37° C. is sucked into the syringe through the tube *a*. After turning the valve *v* it can be ejected on lowering the plunger through the tube *b*, which ends in the hypodermic needle *n*. The needle is inserted into the ear vein of a rabbit and is held in place by a couple of small artery forceps. As the acid is injected intravenously, one observes the normally alkaline urine of the rabbit to turn acid, and as this acidity rises, albumin appears in the urine. The following experiments dealing with the effects of such intravenous acid injections will serve to illustrate this point. Let it be noted that in addition to the appearance of albumin in the urine, this comes to contain various casts, epithelial cells, blood corpuscles, and hæmoglobin. By comparing the urinary output in these animals with that shown by normal animals, as detailed further on, it is evident that this is decreased. Evidences of an œdema are also not wanting; animals injected with an acid do not excrete the water that is injected with

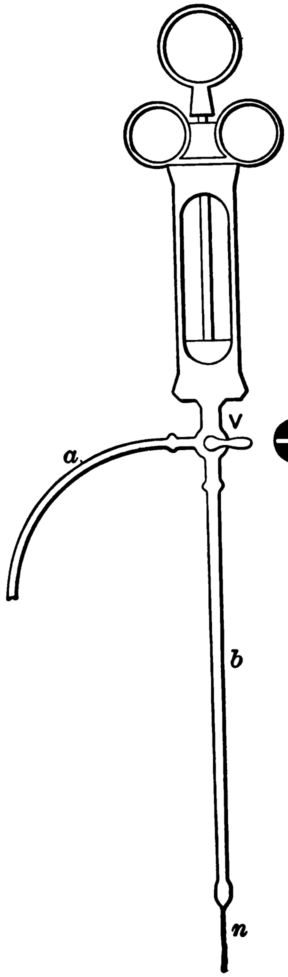

Fig. 9.

this acid as does a normal animal that is given water only. The water when injected *with an acid* is retained in the body, but to this phase of the problem of nephritis we shall need to return later. For the present it is clear that *there develop all the most typical signs of an acute nephritis when acid in sufficient amount is injected into an animal.*

EXPERIMENT 12. — Belgian hare; weight 1870 grams. Has been fed corn, oats, hay, and cabbage. Urine obtained by gentle manual pressure over the bladder.[1] In the time of the experiment there are injected, at 37.0° C. and at a uniform rate, with the exceptions noted, 291 c.c. of the following mixture: 300 c.c. $\frac{1}{20}$ normal HCl + 20 c.c. $\frac{2}{1}$ molecular NaCl.

Time.	Amount of urine in cubic centimeters.	Remarks.
1.20	—	Tied to animal board. No anæsthetic.
1.45	4.0	Turbid, yellow, no albumin, no casts.
2.00	6.0	Injection into ear vein begun.
2.15	Few drops	Turbid, yellow, no albumin, no casts.
2.30	1.9	Clear, yellow, faint trace albumin, no casts.
2.45	—	
3.00	1.5	Clear, brownish tinge, albumin present, few red blood corpuscles, isolated kidney cells, no casts.
3.15	1.6	Smoky urine, albumin, isolated granular and epithelial casts.
3.30	1.3	
3.45	2.2	Smoky urine, albumin, isolated granular and epithelial casts. Injection interrupted for 2¼ min.
4.00	4.8	Smoky urine, albumin, isolated granular and epithelial casts. Injection interrupted for 5 min.
4.15	21.0	Smoky urine, albumin, isolated granular and epithelial casts. Hæmoglobinuria. Injection interrupted for 10 minutes.
4.45		
5.00		Animal dies.

Total urine secreted since beginning injection 34.3 c.c.

Autopsy. — Weight of animal 2135 grams! No free fluid in peritoneal, pericardial, or pleural cavities. Kidneys slightly bluish, and bleed freely on section. Nothing about them is strikingly abnormal.

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[1] In these experiments on albuminuria the *greatest care* is necessary not to injure the lower urinary passages and so get a bleeding that might,

Experiment 13. — Belgian hare; weight 2008 grams. Has been fed a mixed diet of corn, oats, hay, and cabbage. Urine obtained by gentle pressure over bladder. During the course of the experiment there are injected at 37.0° C., and at a uniform rate with the exception noted, 90 c.c. of the following mixture: 90 c.c. $\frac{1}{10}$ normal HCl plus 6 c.c. $\frac{2}{1}$ molecular NaCl.

Time.	Amount of urine in cubic centimeters.	Remarks.
3.35	—	Tied down. No anæsthetic.
3.40	—	Injection into ear vein begun.
3.55	6.0	Turbid, yellow, alkaline to litmus. No albuminuria, no casts.
4.05	1.7	Clearer, trace of albumin present.
4.20	0.8	Urine smoky, albumin increasing. Injection stopped for 15 minutes as animal threatens to die.
4.40		Injection recommenced.
4.45	Few drops	Bloody, much albumin, red blood corpuscles are present, filled with granular casts of various sizes.
4.47		Animal dies.

Total urine secreted since commencing injection 8.5 c.c. (+)

Autopsy. — Weight 2087.5. No free fluid in the peritoneal, pleural, or pericardial cavities. Kidneys slightly swelled. Under the capsule appear tiny hæmorrhagic points.

through the presence of albumin and blood in the urine, lead to the erroneous conclusion that a nephritis is at hand when only some bleeding is occurring into the bladder or urethra. Manual pressure over the bladder must be made with gentleness, and care must be taken not to so crowd the bladder into the pelvis as to kink the urethra. Only the smallest soft rubber catheter, well vaselined, must be introduced. If these precautions are not followed, fallacious, if not worthless, results are obtained. When an animal dies or is killed, the lower urinary passages must be examined for hæmorrhagic points.

Experiment 14. — Belgian hare; weight 2259 grams. Diet unknown, as he has just been received in the laboratory. Urine obtained with a catheter. In the course of the experiment 75 c.c. of the following solution are injected at a uniform rate, with the exception noted: 75 c.c. $\frac{1}{10}$ normal HCl plus 5 c.c. $\frac{2}{1}$ molecular NaCl.

Time.	Amount of urine in cubic centimeters.	Remarks.
11.30	7.0	Tied to animal board. Urine thick, chrome yellow, no albumin.
11.45	19.4	Thick, chrome yellow, no albumin, alkaline to litmus paper. Injection into vein of ear begun.
12.00	2.0	Thick, chrome yellow, no albumin, alkaline to litmus.
12.15	0.4	
12.30	1.6	Clearer, pinkish tinge, albumin present.
12.40		Injection stopped entirely.
12.45	3.7	Urine distinctly red, much albumin, many casts.
1.45	11.5	Urine turbid, red, shows spectrum of oxyhæmoglobin, filled with albumin, casts, (epithelial, granular, and mixed) epithelial cells, and red blood corpuscles. Animal released in good condition, returned to hutch.

Total urine secreted since beginning injection 19.2 c.c.

5.30 Next morning	5.0 per catheter.	Clear, yellow, acid. Casts and albumin still present.
11.00	37.0 per catheter.	Dark amber, thick, faintly acid, clear. Microscopic examination shows many squamous epithelial cells and isolated casts. Carefully filtered urine shows a trace of albumin.

It so happens that the sum total of the chemical changes that go on in the living animal organism are of such a character as to threaten the normally neutral reaction existing in the tissues chiefly from the acid side. Even under normal conditions, the tissues have to guard themselves against becoming acid in reaction. Do we not have to count carbonic acid among the chief end products of the oxidation of our foodstuffs? This normal tendency of the tissues to become acid in reaction is enormously increased under various pathological conditions, and as we shall find these conditions to be just such as are likely to lead to a nephritis, the discussion of this subject will naturally tend to center about a discussion of the conditions which favor such an abnormal production or accumulation of acids in the tissues. An abnormally high *alkali* content in the cells under normal circumstances is scarcely possible, and when it is induced artificially it is difficult to maintain, for the normal acid production (CO_2 production) in the living cell tends quickly to neutralize it. The question of an abnormally high alkali content of the cells is therefore scarcely to be considered in our further discussion of the problem of nephritis. And yet from a theoretical standpoint it is quite as important as that upon which we shall lay the greater stress. As we pointed out in our discussion of the "solution" of colloidal protein gels (such as fibrin or gelatine) these colloids go into "solution" quite as readily in alkalies as in acids. Therefore, even though an abnormally high alkali content is scarcely to be considered as a cause of "nephritis" in living animals (except in cases of poisoning with alkalies) *we should, on the basis of our colloidal conceptions of nephritis, be able to induce this condition experimentally almost as easily through alkalies as through acids.* As the following experiments show, this is actually the case.

Experiment 15. — Belgian hare; weight 2085 grams. Has been fed hay, oats, corn, and cabbage. In the course of the experiment there are injected intravenously at a uniform rate 125 c.c. of the following mixture: 150 c.c. $\frac{1}{10}$ normal NaOH plus 10 c.c. $\frac{2}{1}$ molecular NaCl.

Time.	Amount of urine in cubic centimeters.	Remarks.
2.35	31.	Catheterized. Dark amber, acid to litmus paper. No albumin. No casts.
3.15	0.7	Catheterized. Weighed. Placed in animal board. Injection into ear begun. No albumin. No casts. Acid in reaction.
3.30	1.2	Urine clearer. Acid in reaction (?). Trace of albumin (?).
3.45	8.4	Milky, alkaline to litmus. Faint trace of albumin.
4.00	6.0	Milky, alkaline to litmus. Also isolated casts. Faint trace of albumin.
4.15	1.2	Milky, alkaline to litmus. More albumin. Many long hyaline casts with coarsely granular material sticking to them.
4.30 4.45	0.7 0.4	Milky, alkaline to litmus. Much albumin. Filled with casts. Bloody tinge to urine.
4.58	0.4+	Milky, alkaline to litmus. Much albumin. Filled with casts. Bloody tinge to urine. Animal dies.
	0.6 contained in catheter.	1.0 gram of fæces lost. It is noted that the albumin reactions as obtained with cold nitric acid applied to the filtered acidified urine are not as intense as in the albuminurias induced by acid injections. (Less albumin ?).

Total urine since beginning injection 18.9 c.c.

Autopsy. — Weight 2187 grams! No fluid in the cavities. Intestinal contents seem somewhat more fluid than usual. Kidneys are firm, apparently somewhat swelled, and do not bleed easily.

Experiment 16. — White rabbit; weight 1911 grams. Fed hay, oats, corn, and greens. In the course of the experiment there are injected at a uniform rate 185 c.c. of the following mixture: 225 c.c. $\frac{1}{10}$ normal NaOH plus 15 c.c. $\frac{2}{1}$ molecular NaCl.

Time.	Amount of urine in cubic centimeters.	Remarks.
2.15	85.	Catheterized. Turbid, dark amber, acid. No albumin, no casts.
2.30	0.7	Turbid, dark amber, acid. No albumin, no casts.
2.45	0.7	Weighed. Injection into ear vein begun.
3.00	0.2	Urine as before.
3.15	1.0	Neutral to litmus. Clearer. Small amount of albumin. Many hyaline casts. Some have coarse granules in them.
3.30	6.4	Urine clear as water. Many hyaline casts. Some have coarse granules in them.
3.45	15.5	Urine clear as water. Only a few casts can be found. Albumin present.
4.00	22.0	Weakly alkaline. Albumin present. Isolated casts only can be found.
4.15	24.5	Albumin present. No casts can be found. The urine has a pink tinge (hæmoglobinuria). No red blood corpuscles microscopically.
4.25	....	Injection stopped.
4.30	23.0	Faintly alkaline. Clear, pink, no casts, no red blood corpuscles. Albumin present. Animal released. Seems entirely normal, and eats at once. Weight 2000 grams!

Experiment 17. — White rabbit; weight 2177 grams. Fed hay, oats, corn, and cabbage. In the course of the experiment there are injected at a uniform rate 240 c.c. of the following mixture: 225 c.c. $\frac{1}{10}$ normal NaOH plus 15 c.c. $\frac{2}{1}$ molecular NaCl. Injection made into ear vein.

Time.	Amount of urine in cubic centimeters.	Remarks.
1.50	10.0	Catheterized. Turbid, yellow urine. No albumin. No casts.
2.00		Weighed.
2.15	1 drop	No albumin. Injection begun.
2.30	—	
2.45	0.2	Albumin present. Filled with casts, mainly hyaline in character, but some are finely granular. Much squamous epithelium and cell detritus.
3.00	0.5	Alkaline to litmus. Albumin and casts as before, but all the casts are hyaline except for coarse, granular material contained in or attached to some.
3.15	0.2	Strongly alkaline. Albumin and casts as before.
3.30	2 drops	Strongly alkaline. Albumin and casts as before. The urine has a pinkish tinge (hæmoglobinuria).
3.45	1.0	Strongly alkaline. Albumin and casts as before. Urine pinkish (hæmoglobinuria). Red blood corpuscles are found and two microscopic blood coagula. This bleeding is attributed to traumatism (animal struggled and whipped catheter about).
4.00	2.8	Urine strongly alkaline. The animal has begun to shiver (acid production!) during the last 15 minutes. The previously warm ears are pale and cold.
4.15	13.0	The urine becomes faintly alkaline, then scarcely affects either red or blue litmus. The urine is clear like water except for a clouding due to (traumatic) blood. Careful search of the sedimented urine reveals only an occasional cast. The animal is shivering constantly. It is killed.
4.30	12.0	
4.45	16.0	
5.00	19.0	
5.15	23.0	

Total urine since beginning injection, 87.7 c.c.

Autopsy. — Weight 2326 grams! The peritoneal, pleural, and pericardial cavities are dry. The kidneys are soft and bleed a normal amount. A few pinpoint hæmorrhagic spots are found in the bladder.

2. We need not, however, go outside of the body in order to get a sufficient amount of acid to so upset our neutrality mechanism in the kidney as to lead to an albuminuria. As is well known, large amounts of acid (especially lactic acid) are produced in the muscles when these contract. If the muscle works under physiological conditions and not too fast, the acid as formed may be largely oxidized in situ. But if the muscle works more rapidly then more acid is produced than can be oxidized in the muscles and so in the higher animals some passes unchanged into the blood, with this to the kidneys, and then out in the urine.[1] It is evident that the opportunities for such an accumulation of acid in the body become the greater the more rapidly and the harder the musculature of the body works, and we should add, the more defective the oxygen supply to the working muscles, for this element is necessary for the proper oxidation of the acid in the body. Now such a combination of hard work with a (temporarily) defective oxygen supply to the active muscles is furnished whenever the organism engages in exercise that calls for more than usual effort. We are therefore not surprised to find that soldiers after prolonged marches, women in labor, Marathon runners, etc., give evidences of an albuminuria when examined after such exertions.[2] The amount of exercise needed to bring about such albuminurias is really surprisingly low, as is indicated by the following:

EXPERIMENT 18. — Seven trained athletes just before entering upon a game of basket ball were asked to void their urine into a series of flasks. At the end of the game which lasted one and a half hours they voided their urine a second time into a second series of flasks. *Heller's* test was then applied to the various specimens of urine. *While none of the players showed any trace of albumin in his urine before the play, all gave strikingly marked reactions after the game.* The results of the tests applied to the urines voided after the game are shown in Figs. 10 and 11. The first four tubes are photographed against a white background, the three of Fig. 11 against a black. The faint albumin ring present in the tube on the extreme right of Fig. 11 scarcely shows in the photograph. Interestingly enough, this specimen of urine came from a player who was in the game but five minutes.

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[1] *Trasaburo Araki:* Zeitschr. f. physiol. Chemie, **19**, 422 (1894), where references to his earlier papers may be found; *Hoppe-Seyler, ibid* **19**, 476 (1894); *Fletcher* and *Hopkins*, Journal of Physiology, **35**, 247 (1907).

[2] *W. Leube:* Virchow's Arch., **72**, 145 (1878); *G. Edlefsen:* Centralbt. f. d. med. Wissensch., 762 (1879); *C. von Noorden:* Arch. f. klin. Med., **38**, 205 (1886).

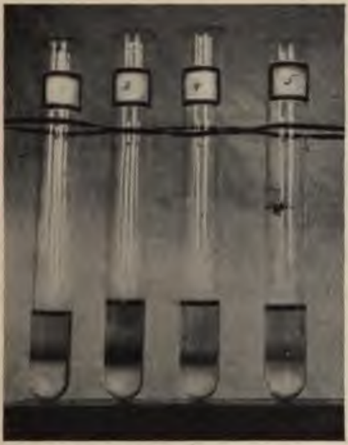

FIG. 10.

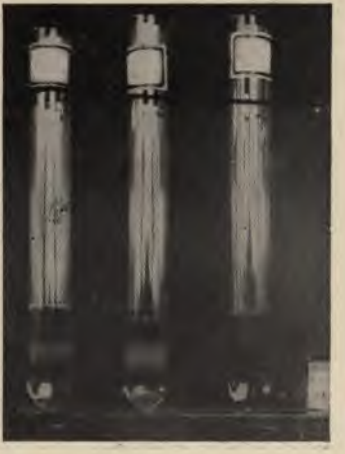

FIG. 11.

EXPERIMENT 19. — Five trained athletes shortly before engaging in a match game of basket ball void their urine into a series of flasks. All the urine voided during the succeeding 1½ hours during which the game is played is collected in a parallel series of flasks. In none of the control urines with the exception of that of Player IV are there found albumin or casts. This player had found it necessary before coming to the game to rush about town making train and street-car connections and had moreover had a "cold" for three days previously. After the game all the players showed an albuminuria and a great many granular, hyaline, and mixed casts. The albumin and the casts in the previously affected individual were markedly increased. The findings are illustrated in Fig. 12 and in the appended Table III.

The five tubes on the right show the results of applying the cold nitric acid test to the urine after the game. The tube on the extreme left shows the albuminuria existing in Player IV even before entering the game. The quantitative estimations in the *Esbach* tubes were carried out in the ordinary way using *Tsuchiya's*[1] phosphotungstic acid reagent. The photograph was made after the tubes had stood for only 6 hours. The readings in the table were made after 24 hours.

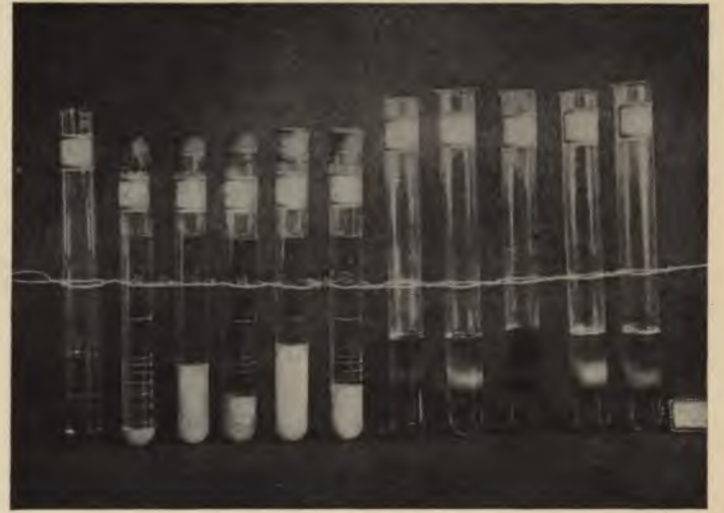

FIG. 12.

TABLE III.

BEFORE THE GAME.

Player	Amount of urine in cubic centimeters.	Nitric acid test.	Casts.
I	60	Negative	None
II	158		
III	5		
IV	47	Positive	Occasional granular and hyaline
V	134	Negative	None

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[1] *Tsuchiya:* Centralbl. f. inn. Med., **29,** 105 (1908).
Phosphotungstic acid, 1.5 grams.
Concentrated hydrochloric acid, 5.0 c.c.
Alcohol to make, 100.0 c.c.

After the Game (1½ Hour Period).

Player.	Amount of urine in cubic centimeters.	Nitric acid test.	Casts.	*Esbach* reading with phosphotungstic acid.	Albumin excreted in grams.
I	168	Positive	Many hyaline, granular, and mixed casts present in all.	0.6	0.111
II	69			3.25	0.224
III	35			2.3	0.080
IV	30			5.0	0.150
V	94			2.75	0.258
					Av. 0.163

A remarkably short period of hard athletic work suffices to produce a great albuminuria, as the following taken from many such observations shows:

Experiment 20. — B——, a well-trained and expert University runner ran a quarter-mile race. Before starting he voided 54 c.c. of urine which on examination showed no albumin. After his race (time: 58 seconds!) he voided 59 c.c. of urine in which much albumin was found. In Fig. 13 are shown the results of the albumin tests as applied to the two samples of urine. In the two tubes on the right the cold nitric acid test has been applied to the urines; in the tube on the left a quantitative estimation has been carried out in an *Esbach* tube with *Tsuchiya's* phosphotungstic acid reagent.

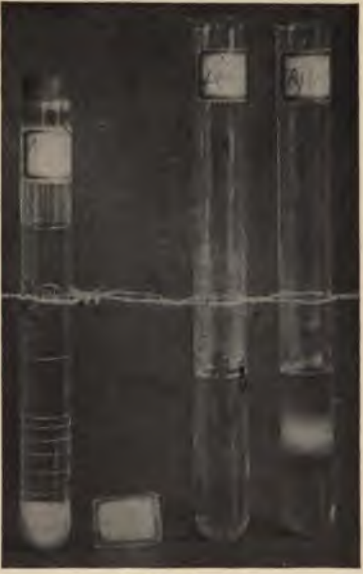

Fig. 13.

3. A condition in the body entirely analogous to that produced voluntarily by the athlete in his athletic activities is created through any *uncompensated heart lesion or any disease of the lung* of such a character as to materially interfere with the proper aëration of the blood. Either of these

conditions interferes with the proper escape of carbon dioxide from the blood (and so from the cells in which this is produced).[1] But they do more than this, they place the organism as a whole in a state of lack of oxygen, and as a necessary consequence of this we know from the studies of *Trasaburo Araki*,[2] *Hermann Zillessen*,[3] and *P. von Terray*[4] that we get an abnormal production and accumulation of other acids, notably lactic and oxalic acids, in the tissues. Heart or lung lesions therefore are potent to lead to that same abnormally high acid content of the cells of the kidney that we previously found created through the direct injection of acids, or the hard work of the athlete, and so we are prepared to find in these pathological states of the heart and lung that albuminuria is again a common consequence. As a matter of fact the association of "nephritis" or "*Bright's* disease" with heart lesions of the most varied kinds, or pathological conditions in the lung (manual compression of the thorax, pleurisy with effusion) that reduce its ventilation area sufficiently, is so constantly observed that it is taken for granted clinically.

4. It requires no special comment to recognize that a whole series of pathological states such as the severer anæmias, carbon monoxide poisoning,[5] and epileptic seizures, which at first sight seem to have nothing in common with each other, contain within themselves all the elements necessary for the development of an albuminuria. The severe anæmias (leukæmia or pernicious anæmia) merely constitute further ways of interfering with a proper oxygen

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[1] *Strassburg:* Pflüger's Arch., **6**, 94 (1873); *A. Ewald:* Arch. f. (Anat. und) Physiol., 663 (1873); 123 (1876).

[2] *T. Araki:* Zeitschr. f. physiol. Chemie, **15**, 335 and 546 (1891); **16**, 453 (1892); **17**, 311 (1893); **19**, 422 (1894).

[3] *H. Zillessen:* Zeitschr. f. physiol. Chemie, **15**, 387 (1891).

[4] *P. von Terray:* Pflüger's Arch., **65**, 393 (1896).

[5] *G. Thompson:* Trans. Assoc. Am. Physicians, 1902; *William Ravine:* Personal Communication.

supply to the tissues. Both are accompanied by an abnormal storage and production of acid in the tissues as evidenced by *Felix Hoppe-Seyler's*[1] and *T. Irasawa's*[2] chemical analysis of the urine, and *R. von Jaksch's*[3] titrations of the blood in cases of severe anæmia. An abnormal acid production in carbon monoxide poisoning has been proved by *T. Araki*,[4] *E. Münzer* and *P. Palma*;[5] in epilepsy (severe muscular exertion with defective breathing) by *Araki* and *E. Mendel*. As clinicians well know, the existence of an albuminuria in any of these pathological states is usual.

5. The ætiological importance of "cold" (in the strict sense of the word as a lowering of the body temperature and unaccompanied by an infection) in the production of an acute nephritis, or in the lighting up of a chronic one that has slumbered for a time, has always been insisted upon by the older observers. This view finds a rigid scientific support in our present knowledge of the physiological effects of low temperature upon the warm-blooded animals. Of these none is more characteristic than the rise in the acid content of the cells of an animal so exposed.[6] In this

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[1] *F. Hoppe-Seyler:* Zeitschr. f. physiol. Chemie, **19**, 473 (1894).

[2] *T. Irasawa:* Zeitschr. f. physiol. Chemie, **15**, 380 (1891).

[3] *R. von Jaksch:* Klinische Diagnostik, Fünfte Aufl. **2**. Berlin, 1901.

[4] *T. Araki:* Zeitschr. f. physiol. Chemie, **15**, 335 (1891).

[5] *E. Münzer* and *P. Palma:* Prager Zeitschr. f. Heilk, **15**, (1894).

[6] See *Araki:* Zeitschr. f. physiol. Chemie, **16**, 453 (1892). On the basis of this same acid production we can with the greatest ease explain the precipitation of an attack of hæmoglobinuria in the cases of so-called paroxysmal hæmoglobinuria when these patients take a cold bath, are exposed to cold, etc. The acid produced under these circumstances rises to the point where it leads to a hæmolysis of the patient's red blood corpuscles. This view is supported by the fact that it is possible to precipitate an attack of hæmoglobinuria for diagnostic purposes quite as easily through temporary obstruction of the circulation in the arm by applying a band about it (accumulation of carbon dioxide and production of other acids due to a lack of oxygen), as through the customary immersion of the extremities in cold water. The essential nature of the paroxysmal hæmoglobinurias would seem to reside in the lesser resistance which the red blood corpuscles of such

way do we find a ready explanation of why such trivial exposure to cold as is produced by a cold bath leads, in not a few individuals, to the appearance of albumin in the urine.

6. Thus far we have discussed only general conditions — conditions affecting the whole animal — that are capable of inducing an abnormal storage or production of acid in the body, and so of inducing an albuminuria. We will now consider a series of more local conditions that bring about the same result.

Instead of interfering with the normal action of the heart or lungs an effective state of lack of oxygen in the kidney can, of course, be induced by direct interference with the normal blood flow through this organ (see Experiment 33). Experimentally such a condition is easily established by total or partial ligation of either the arterial or the venous blood supply of this organ, a state that has its clinical parallel in such affections as partial or complete occlusion of the renal vessels through arteriosclerosis, thrombosis, embolism, or the pressure of tumors, etc., upon these vessels. But as the experiments of *T. Araki* and *H. Zillessen* have shown such an interference with the normal blood supply (oxygen supply) to any of the parenchymatous organs is followed immediately by the accumulation of acids in the affected tissues. Do we now find that in such local circulatory disturbances of the kidney we get an albuminuria? That we do is, of course, known to everyone — it constitutes, since *Max Herrmann's*[1] experimental studies, one of the

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patients have to such a hæmolytic agent as an acid. The resistance to such a hæmolytic agent is enormously increased by the addition of various salts to the blood, as *Oscar Berghausen* has shown. This fact is not only of theoretical interest, as I have tried to show in discussing the nature of hæmolysis [*Fischer:* Kolloid Zeitschr. **5**, 146 (1909) or Œdema, 166 (New York, 1910)], but of direct therapeutic use in the treatment of these cases of hæmoglobinuria (diet rich in alkalies, administration of calcium salts, etc.).

[1] *Max Herrmann:* Sitzungsber. d. Wiener Acad. Math.-phys. Klasse, **65**, (1861).

classical facts of pathological physiology; it is attested to by the experience of any medical diagnostician; it is the bugbear of surgeons who operate on the kidney and find a temporary closure of the renal vessels expedient or necessary.[1]

7. Instead of interfering directly with the oxygen supply to the kidney by procedures which interfere with the blood supply to this organ, we can bring about the same result in a more subtle way by giving the kidney parenchyma its normal oxygen supply, but by so interfering with the chemistry (enzymatic processes) of the cells themselves that make up the kidney as to render these incapable of utilizing in proper form the oxygen that is freely supplied them. So far as the end result is concerned, it matters little, of course, whether we interfere with the normal oxidation, for example, of the carbohydrates of the living cell into carbon dioxide and water by shutting off the oxygen supply to the cell and so halting the decomposition of the carbohydrates when these have been changed to lactic, oxalic, formic, and other acids (saccharinic acids);[2] or whether we do nothing about the oxygen supply but introduce something into the cell which prevents the oxidation of the lactic acid as formed to carbon dioxide and water (or more probably the mother substance of the lactic acid glycerine aldehyde).[3] The cells of the living body in the

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[1] For a discussion of the methods to be employed in combating the evil consequences of such temporary closure see Part IV dealing with the treatment of nephritis.

[2] The chemical aspects of this problem of the formation of acids from carbohydrates in the absence of oxygen are discussed by *Felix Hoppe-Seyler:* Berichte d. deut. chem. Gesellsch. **4,** 346 (1871); *H. Kiliani: ibid,* **15,** 701 (1882); *Duclaux:* Compt. rend., **94,** 169; *Schützenberger: ibid,* **76,** 470; *Buchner, Meisenheimer,* and *Schade:* Berichte d. deut. chem. Gesellsch., **39,** 4217 (1906); *J. U. Nef:* Liebig's Annalen, **357,** 214 (1907). The biochemical aspects of this same problem are discussed in the papers on lack of oxygen already referred to on pages 48 and 49.

[3] In this connection see the interesting work of *R. T. Woodyatt:* Journal of the American Medical Association, **55,** 2109 (1910).

end get into the same state whether they have their oxygen supply cut off, or whether this is not interfered with, but they are "poisoned" in such a way as to be unable to utilize this oxygen as normally.

As has been shown particularly well by *T. Araki*, a large number of poisons lead to the same state of lack of oxygen, with its associated abnormal production and accumulation of acids in the tissues, as do the grosser interferences with the oxygen supply to the various organs or the body as a whole, that have already been described. And so it cannot surprise us to discover that *Araki's list of poisons — poisons utilized to show that an abnormal acid production is the constant accompaniment of a state of lack of oxygen in the tissues no matter how produced — is identical with the list of poisons familiar to any laboratory or clinical worker who has busied himself with the problem of the toxic nephritides:* metallic salts, such as those of arsenic, uranium, chromium, and lead; alkaloids, such as morphine, cocaine, and strychnine; anæsthetics, such as alcohol, ether, and chloroform; unclassified poisons, such as amyl nitrite, the cyanides, and phosphorus.

8. In concluding this section we need to discuss the albuminurias encountered in three conditions which not only are readily interpretable on the basis of our contention that albuminuria results whenever abnormally great amounts of acid accumulate in the kidney but give this contention valuable support.

Since *Rudolph Virchow's* description of the condition fifty years ago, the *albuminuria of the newborn* constitutes a matter of common knowledge to every pædiatrist. It occurs in perfectly healthy infants as a transitory phenomenon, is regarded as "physiological," and to it ordinarily no clinical importance is attached. Whence comes it? The condition is most commonly found in "hard" labors, when the cord prolapses, in breech presentations, etc., all of them conditions which mean a state of more than the normal lack of oxygen in the organism of the child during the process of its birth. Even normal labor means of course a decided interference with the circulation of the infant, — is it not in this fact and the associated accumulation of carbon dioxide and other acids in the blood that the cause of the first respiration is to be sought, as *Zuntz* has shown? Difficult labors mean in toto only a more than usual interference with the circulation of the child. It is entirely a matter of definition as to just how much of this we will accept as " physiological." But when we have thus connected the development of the albuminuria with a disturbance in the general circulation of the child then we have made it, at the same time, a mere subheading of the albuminurias discussed in paragraph 3 of this section (page 47), and the albuminuria is " physiological " only as we will accept little or great interference with the circulation in the infant during its birth as " physiological."

Albuminuria is the constant *accompaniment of salt starvation*, be this a complete salt starvation or only such a partial one as is induced by eliminating completely the sodium chloride from the food. Under this same heading is to be classed the albuminuria consequent upon the *excessive consumption of water* low in salts. The latter washes the salts out of the body (see Section 4 of Part III) and so leads indirectly to the same state as that induced by a lack of salts in the diet. The effect of a salt-free diet is twofold. In the first place it leads to the accumulation of acids in the tissues.[1] Other things being equal, we have on this basis alone therefore a reason for the albumin going into solution (and so an albuminuria) when salts are withheld from the diet. But the salts act in yet another way. We found, in detailing the experiments on the "solution" of fibrin and of gelatine in acids, that this tendency of the colloidal gels to go into solution in a given concentration of acid is greatly inhibited through the presence of all salts, even neutral salts incapable of an effect that might be construed as due to a mere neutralization of the acid. Through the withdrawal of salts from the tissues, whether by salt starvation or through leaching these out with water, we favor therefore the tendency of the proteins to go into solution in two ways: not only do we render possible an abnormal production or accumulation of acids in the tissues, but we take away at the same time the effect of the salts in reducing the tendency of the colloids to go into solution in such acids as may be abnormally present, or those which, like carbon dioxide, are normally produced in the tissues.

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[1] *G. Bunge:* Zeitschr. f. Biol., **10,** 111 (1874); see also *J. Forster: ibid,* **9,** 297, 369 (1873); *N. Lunin:* Zeitschr. f. physiol. Chemie, **5,** 31 (1881).

9. If now albuminuria represents merely that simple "solution" of the albumin of the kidney substance itself in the urine, or if, in other words, it does not come from the blood (except in that indirect way in which the proteins of any cell come originally from the blood), then albuminuria cannot be that strange and specific thing which as clinicians we are likely to make it. *Any cell must, under conditions similar to those existing in the cells of the kidney when this is nephritic, be capable of serving as a source of albumin to a surrounding liquid medium, and so be capable of being responsible for a state which in the kidney goes by the name of "albuminuria."* A little thought will show that such actually is the case.

Any worker in the biological sciences is familiar with the ancient fact that "dead" organisms, be these unicellular or multicellular, allow the escape of albumin from them. A frog or fish living in his aquarium does not impart an albumin reaction to the water in which he lives. But let him die and in a few hours the previously clear water gives a positive result when tested for albumin, and this reaction becomes the more intense as time goes on. What happens is, of course, that after death the tissues become acid in reaction, and so some of the protein now goes into "solution" in the surrounding medium.

But we need not wander so far away from the mammals, or in fact the living animal itself, in order to show that "albuminuria" is not the specific thing we think it. As surgeons well know, the normal intestinal juices scarcely yield an albumin test, yet the fluid contained in a strangulated hernia or a volvulus is rich in albumin. Here the interference with the circulation to the gut, produced through the strangulation or the twist, has placed a section of the bowel in a state of lack of oxygen; it develops in consequence an abnormally high acid content, and so some of the proteins of the gut wall go into "solution" — in other words, we get in the bowel what in the kidney is called albuminuria.

Analogous conditions exist for any of the parenchymatous organs. When any organ is placed under conditions which lead to an increase in its acid content, a state analogous to the albuminuria of the kidney results. The lymph coming from a muscle that is made to work hard has a higher albumin content than that coming from this same muscle when at rest, and when the circulation through the liver is impeded (I should say oxygen supply through the hepatic artery is interfered with), either through ligation of the inferior vena cava or obturation of the thoracic aorta, the albumin content of the lymph coming from this organ begins to rise as *E. H. Starling*[1] has clearly shown.

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[1] *E. H. Starling:* Jour. of Physiology, **16**, 224 (1894); **17**, 30 (1895); see also *Bayliss* and *Starling: ibid*, **16**, 159 (1894).

II. THE MORPHOLOGICAL CHANGES IN THE KIDNEY.

1. Introduction.

Anyone who has on the one hand busied himself with the clinical, or as we might better say, the biochemical, aspects of nephritis, on the other with the morphological aspects of this same problem, as this has been developed for us during the last two or three decades, must be struck not alone by the fact that the two have grown up practically independently of each other, but that they have made but slight effort to find common ground.

As a matter of fact, when we attempt to find a connection between the comparatively simple biochemical characteristics of nephritis and the elaborate morphological analyses of the organs from patients who have clinically shown the biochemical marks of a nephritis, this is at first sight not easy. Even if we ignore the fact that much of that which is supposed to characterize nephritis morphologically has nothing to do with the albuminuria, the changes in the secretion of water, the changes in the secretion of dissolved substances, etc., which are the distinguishing marks of a nephritis biochemically, there still remains an apparent lack of connection between the facts, to which any clinician or pathologist will testify, namely, that individuals may die of an acute *Bright's* disease and show surprisingly little macroscopic or microscopic change in the kidney, while others, never affected with any symptoms referable to the urinary system, may show on autopsy the infant-sized kidneys of chronic interstitial nephritis. And yet if we will but free our minds from the erroneous conclusions to which the temptations of elaborate fixing and staining methods and high power microscopes have led us, it is an easy matter to see that all the morphological changes that occur in a kidney, the seat of an acute or chronic nephritis, are fundamentally simple in character, and that they are easily brought into connection with the clinical manifestations of the disease. We will discover at the same time that the essential morphological changes of acute and chronic nephritis were recognized and a satisfactory classification of the nephritides on morphological grounds was made decades ago, more especially by *Weigert*,[1] and that a classification of the nephritides on the basis of pathological physiology brings us in these modern days back to yet older teachings, to those of *Frerichs*,[2] for example, who regarded all the nephritides to be in essence the same.

The morphological changes that occur in the kidney, which any pathologist will accept as characteristic of *the acute forms of nephritis*, and for the recognition of which no elaborate histological technique is at all necessary, are:

1. An increase in the size of the kidney, traceable on the examination of fresh, unfixed, and unstained cells, back to an increase in the size of the individual cells and tissues composing the kidney.

2. A loss of the normal color of parts or all of the kidney which assume a less glistening, drier, and more opaque (boiled) look. On microscopic examination this change is found to be associated with the appearance of granular substances in the cells of the affected portions of the kidney. This change in color, taken in conjunction with the increase in the size of the kidney, constitutes the "cloudy swelling" of the pathologists.

3. The appearance of blood corpuscles extravascularly.

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[1] The most accessible of *Weigert's* papers on nephritis appear in Virchow's Archiv during the years 1860 to 1875.

[2] *Frerichs:* Die Bright'sche Nierenkrankheit. Braunschweig, 1851.

They may be found in the tissues of the kidney itself, or in the spaces about the glomerular tufts and in the uriniferous tubules.

4. Evidences of a falling apart of the kidney as a whole and of a disintegration of the individual cells of the kidney. Under this heading are grouped not only the gross destructive lesions observed in the kidney, such as the rupture of capillary tufts, but the separation of individual and groups of cells from their attachments in the glomeruli, *Bowman's* capsule and the uriniferous tubules (formation of casts).

This catalogue of morphological changes as given for acute nephritis, or as we might better call it acute parenchymatous nephritis, holds with but small modification for the chronic parenchymatous forms also. The chronic forms show all the changes of the acute with certain others added to them, notably a "fatty degeneration," and the development of a certain amount of scar tissue. But where are we to put the chronic interstitial type of nephritis?

2. The Relation Morphologically of the So-called Chronic Interstitial Nephritis to the Parenchymatous Types.

The most apparent difference between the parenchymatous forms of nephritis and the chronic interstitial resides in the difference in the comparative sizes of the organs as a whole in the two conditions. While the former is larger than normal, the latter is smaller. And yet this does not constitute the most characteristic difference between the two. This is rather to be sought in the way in which the two pathological states are brought about.

In the frankly parenchymatous forms of nephritis the whole kidney is usually affected at once and, on the whole, equally. If the kidney cells are sufficiently damaged, and the patient dies, we find on autopsy the familiar large kidney.

In chronic interstitial nephritis the ultimate picture is produced through a gradual but complete destruction of one piece after another of the kidney parenchyma, with replacement of the defect with connective tissue. *The portions of kidney involved in this localized destruction of kidney parenchyma show all the signs characteristic of parenchymatous nephritis.* Between these localized areas of parenchymatous nephritis the kidney tissue is healthy. When, now, we remember that less than one-third of the total kidney substance is necessary for the maintenance of life, it is easy to see why a patient with chronic interstitial nephritis runs along in a fairly normal way. The destruction of the kidney occurs so very slowly that little albumin appears in the urine, and casts only in small numbers. So the patient may die without his kidney state ever having been recognized, or the symptoms of intoxication characteristic of removal of kidney substance down to the physiological minimum may be the first to draw our attention to the pathological state, clinically.

We shall have occasion to return to all this later. For the present it is sufficient to merely emphasize the fact that a *chronic interstitial nephritis is in essence also a parenchymatous nephritis, — a slow-going but progressive localized parenchymatous nephritis resulting in death and loss of the involved portions of the kidney, and resulting ultimately in a picture which is best described by calling it an atrophy of the kidney.* The patient with chronic interstitial nephritis is, therefore, in the same position as an animal that has had its kidney substance progressively diminished in amount by successive operations and ablations of kidney parenchyma. The man who has gone through life without signs or symptoms of kidney disease, who dies of other causes than kidney disease and shows on the autopsy table what, as *morphologists*, we call chronic interstitial nephritis, is simply like the animal that has suffered a great reduction in total kidney substance, but has not yet reached the physiological minimum compatible with life for that animal under the conditions under which it has to live. What is left of kidney parenchyma to man or animal is still physiologically active and physiologically adequate. Such a biological contention finds its morphological support in the fact that the parenchyma of such (morphologically) chronic interstitial types of nephritis shows little or no change either macroscopically or microscopically ("small red kidney"). The presence of the connective tissue in the kidney is an accident, it is scar tissue, and whatever importance we may care to attach to it morphologically, this is no more any indication of the physiological state of the kidney parenchyma that is left than the scar which repairs and serves to reunite the ruptured ends of a muscle is any index of the physiological efficiency of that muscle.

With this we have disposed of the apparent difference between parenchymatous nephritis and what is called chronic interstitial nephritis so far as differences in the sizes of the kidney as a whole are concerned. At the same time we have indicated why what parenchyma is left in the (morphologically) chronic interstitial nephritis may look fairly normal both macroscopically and microscopically. *Not until larger portions of the kidney, or maybe all that is left of the organ, shows the changes characteristic of the parenchymatous types of nephritis ("small gray kidney"), do we have added to the morphological picture of chronic interstitial nephritis, as already described, the increase in the size and changes in the color of the individual cells of the kidney, and franker evidence of albumin, blood, and casts in the urine, as listed above, in discussing the parenchymatous types of nephritis.*

In thus getting the chronic interstitial forms of nephritis back into a group with the frankly parenchymatous forms, one point remains undiscussed, and that is the association of an œdema and a diminished secretion of urine with the one form, while a lack of œdema and an (so-called) increased urinary output go with the other. But these physiological phenomena can also be easily explained, as will be done later.

Let us now discuss the morphological changes observed in the nephritic kidney as listed above, seriatim.

3. The Changes in the Size and in the Color of the Kidney in Nephritis (Cloudy Swelling).[1]

§ 1.

While we shall later find ourselves compelled to discuss these two changes in the kidney separately, we will first take them up together because it is in this form, under the caption of *cloudy swelling*, that they have been chiefly discussed by the pathologists.

As is familiarly known, we are indebted to *Rudolph Virchow* not alone for a first clean-cut description of this cloudy swelling as it occurs in the kidney (and other parenchymatous organs), but for a first attempt to analyze its nature. *Virchow* held cloudy swelling to be "a kind of acute hypertrophy with tendency to degeneration," a phrase which has found its way into even our most modern textbooks of pathology. But while such a phrase still serves many as a satisfactory characterization of the condition from a biological standpoint, it means nothing, of course, from the standpoint of its physicochemical analysis. Toward the physicochemical analysis of cloudy swelling *Virchow* contributed the important suggestion that the cause of the granule formation in the cells is due to a change in their albuminous constitution. He based this conclusion upon the fact that the granules are soluble in acids and alkalies, and not in ether, thereby distinguishing them from fat deposits in the cells (fatty degeneration) which at times mimic in general appearance cells affected with cloudy swelling. For the increase in the size of the cells *Virchow* gave only the biological explanation of an "increased irritation" of the affected cells, caused for example by the products of an infectious disease, in consequence of which they were made to take up "excessive amounts of nutrient material."

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[1] *Martin H. Fischer:* Kolloid Zeitschr., **8**, 159 (1911).

That cloudy swelling represents a change in the albuminous constitution of the cell seems never to have been questioned. *Eduard Rindfleisch*[1] accepted this belief and, moreover, expressed himself of the opinion that cloudy swelling was "passive" in its nature and due to "a kind of corrosive action in consequence of which the albuminous matters, held in solution by the protoplasm, undergo coagulation and become visible as minute granules." In 1882, *Julius Cohnheim*[2] subjected *Virchow's* teachings to a rigorous critique. That the process of cloudy swelling involved the albuminous constituents of the cell he did not question, but he perpetuated a conclusion (erroneous as we shall see) of *Virchow*, when he wrote, "Of course we must deal here with a protein that is different from that which is normally present in the cell protoplasm . . . as we could not otherwise account for the optical difference." But *Cohnheim*, too, expressed the possibility of cloudy swelling representing "a spontaneous precipitation in solid form, or the coagulation of a previously fluid protein."

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[1] *Eduard Rindfleisch:* Pathological Histology. Translated by *Baxter*, 30. London, 1872.

[2] *Julius Cohnheim:* Allgemeine Pathologie, Zweite Auflage **1**, 662; **2**, 570. Berlin, 1882.

What underlies such a change in the albuminous constitution of the cell, he did not attempt to say, but he showed very conclusively that the causes proposed by older writers were questionable if not entirely inadequate. Thus he showed that the fever accompanying the various infections liable to be accompanied by a cloudy swelling could not by itself be the cause of the change, by calling attention to the well-known fact that cloudy swelling may be absent in cases that have run a high fever, or present in conditions not associated with an abnormal rise in temperature.

In such a half-hypothetical state did the subject of cloudy swelling remain until 1901, for in spite of various discussions of the subject, no clear-cut advance was made either toward defining more precisely what cloudy swelling is, nor yet in discovering a something common to all conditions associated with cloudy swelling, which might justly be regarded as its fundamental "cause." At this time *H. J. Hamburger*[1] reported a series of observations on isolated liver, kidney, and spleen cells which served to establish more firmly what can justly be regarded as little more than lucky speculation on the part of the older writers. *Hamburger* applied to these cells some earlier observations made on red and white blood corpuscles. In a study of the latter he had found that various acids, including carbon dioxide, bring about an exchange of substances, including water, between the red and white blood corpuscles and the serum in which they are contained. Under the influence of acids all these cells take up water from their surroundings. He paralleled this with the findings of previous observers that, in fevers of the most varied origins, acids are produced and the "alkalinity" of the blood is reduced, and so concluded that in this acid production resided the cause for the *enlargement* of the cells in cloudy swelling. Just why acids bring about any enlargement he does not state definitely, though changes leading in the aggregate to an increase in the osmotic pressure of the cell contents are held mainly responsible. *Hamburger* then points out that the white opaque *appearance* of isolated kidney, liver, and spleen cells exposed to dilute acids is identical with that of cells affected with cloudy swelling and discovered post mortem. Cells treated with an acid are studded with granules, as are the cells showing a cloudy swelling that are found post mortem, and to prove that the granules are similar in character in both, and represent albumin precipitates, he calls attention to the fact that the granules which he has made appear through a weak acid dissolve again as the acid concentration is increased. An analogue of the production of the granules in the isolated parenchyma cells *Hamburger* found in the precipitation of albumin from a diluted blood serum when an acid is added to this.

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[1] *H. J. Hamburger:* Osmotischer Druck und Ionenlehre, **3**, 49 (Wiesbaden, 1904), where references to his earlier articles may be found. See also *Karl Landsteiner:* Ziegler's Beiträge, **33**, 237 (1903).

The first great value of *Hamburger's* studies resides in the fact that he has detailed experiments which show that all the necessary elements for cloudy swelling reside in the parenchyma cells themselves, and that he has pointed out that what is added through an infectious disease (or as we might say in order to make our contention more pointed, any condition which is capable of inducing a nephritis) may be nothing more than a little acid. This simple reasoning of *Hamburger* does away with the biological terminology that has so long been applied to the subject of cloudy swelling, and renders possible an attack upon the problem in the light of the simpler concepts of physics and chemistry.

Since *Hamburger's* work I know of no contributions to the subject of cloudy swelling which have either questioned the correctness of his view, that the increased absorption of water by the cell affected with cloudy swelling represents an osmotic phenomenon, nor yet any which have adduced further evidence in support of the protein precipitation idea of the granule formation in this condition. As the subject is intimately connected with our problem of the morphological changes occurring in nephritis, I felt that it could to advantage be restudied at this time, especially since the acquisitions of colloid chemistry — the chemistry of the very substances of which the kidney is composed — have furnished us with data and theoretical deductions that are of immediate applicability in the analysis of this problem. By utilizing these we shall find ourselves in a position to give a simpler physicochemical explanation for the increased water absorption by the tissues in cloudy swelling than is contained in the unsatisfactory osmotic explanation of this part of the phenomenon, and at the same time we shall learn how the clouding of the parenchymatous organs follows the same laws as the precipitation of such a simple colloid as casein. In this way we shall find a ready explanation of the first two of the morphological changes in the kidney catalogued above and characteristic of nephritis, namely, the increase in the size of the parenchymatous elements, and their change in color. At the same time we shall find that both arise from the same abnormal production and accumulation of acid in the kidney, — the same condition therefore that we have previously held responsible for the albuminuria.

§ 2.

We shall first describe a series of observations on the artificial production in excised kidneys of the changes characteristic of nephritis (production of cloudy swelling) which will prove themselves of service in the further analysis of our problem. The methods employed in these experiments were the same throughout. The kidneys of healthy, freshly-killed rabbits and guinea pigs were used, which after being sliced were distributed into bowls each containing 100 c.c. of the necessary solutions. As it is impossible to give absolute values to the various grades of grayness and opacity observed in the different solutions, one can, in the description of the findings, only compare the appearance of a tissue in one solution with that of a similar piece in a different solution at the same time. The general conclusions from a long series of experiments may be summarized as follows:

(*a*) When slices of fresh kidney are dropped into distilled water they slowly swell and at the same time become gray. A tone of gray that is readily distinguishable from the color of the normal organ appears over the cut surface some three or four hours after being dropped into the water. This gradually increases in intensity until, twenty-four hours after the beginning of the experiment, the tissues look decidedly gray. For a day or two longer this may continue to increase in intensity, but the change from the first twenty-four hours is not very marked. As the tissue becomes gray it shows an acid reaction to litmus, and this acid production in even a small piece of tissue may be sufficiently great to impart an acid reaction to the surrounding fluid.

(*b*) The pieces of tissue swell much more rapidly if they are placed in any dilute acid instead of in distilled water. This is shown in Fig. 14. *A* has simply been protected against evaporation. *B* has lain for an hour and a half in a 0.003 normal hydrochloric acid solution. The two pictures represent opposite faces of the same cut through the kidney. The tissues also become gray sooner in an acid solution than in distilled water. In 0.005 normal solutions of lactic, formic, acetic, tartaric, hydrochloric, sulphuric, or nitric acids a decided cloudiness is visible in ten minutes after immersion. This cloudiness becomes gradually more marked. After three hours, when the control in distilled water is just showing a grayness, the slices of tissue in the dilute acids are grayer than the controls appear the following day. The various acids show some difference in the intensity of the cloudiness that they produce, but this is so much a function of their concentration and the time that a table of their relative effectiveness cannot be given to advantage. After another two hours the tissues in all the acid solutions are intensely gray. The control in pure water is about as gray as the tissues placed in the dilute acids were after ten minutes of immersion. On the following day an ultimate degree of grayness (a typical "boiled" appearance) is shown by all the organs in the dilute acids.

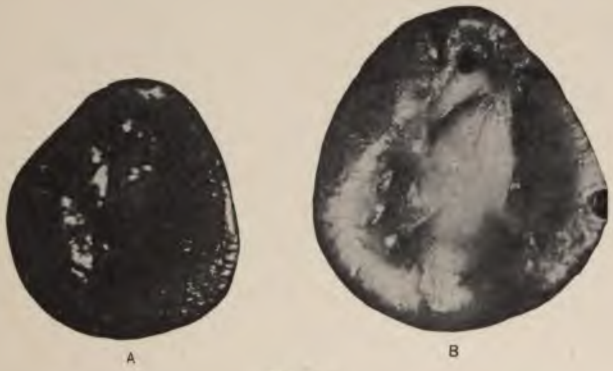

FIG. 14.

Speaking generally, it may be said that when the effects of different concentrations of the same acid are compared, the cloudiness develops the more rapidly the greater the concentration of the acid. So far as intensity is concerned there is, however, little difference. In the end every acid gives the tissues a boiled appearance. With different concentrations of nitric acid I found the boiled appearance after a ten-minute immersion in 0.1 normal acid. In 0.05 normal acid the same appearance was attained in an hour; in 0.025, 0.01, and 0.002 normal in two to three hours.

What has been said of nitric acid holds true in general for all acids, though there are more or less specific differences with the different acids both so far as rapidity of development and intensity of the cloudy swelling is concerned. Acetic acid is particularly interesting. With increasing concentrations of the acid there is first an increase in the rate and (in units of time) in the intensity of the cloudiness produced. If we observe closely, this is seen to be followed with increasing concentrations of acid (above 0.1 normal acetic acid) by a stage in which the cloudiness is *less* than in lower concentrations. To see these successive changes one must observe especially the superficial portions of the tissues. A second clouding can now be obtained by changing to one of the "strong" acids (nitric, sulphuric, or hydrochloric) of the same or of a higher normality than that of the acetic acid which has brought about the disappearance of the first clouding. This change from cloudiness to clearness and back again to cloudiness, with progressive increase in the concentration of an acid, can be followed particularly well under the microscope [see (*g*) below]. But even in the sections of tissue kept in the "stronger" acids can two such regions of cloudiness separated by one of clearness be discerned. I found, for example, that the marked cloudiness of slices of kidney, which had been kept for one and one-half hours in concentrations of nitric acid up to 0.005 normal, disappeared when the surface of the organ was touched with the ordinary weak acetic acid of our laboratory reagents, to reappear when dilute nitric acid was substituted for it.

The cloudiness of the tissues obtained in any of the acids listed above, if developed in not too high concentrations (below 0.005 normal), can also be made to disappear if the tissues are placed in equinormal alkali solutions, or in alkali solutions of a higher concentration.

(*c*) Through the addition of various salts the development of a cloudiness in any *acid* solution can be either retarded or hastened. So far as the absorption of water is concerned, all the salts have but one effect — they decrease the amount of the swelling in the acid solution. When to a 0.005 normal hydrochloric acid solution enough of various potassium salts is added to make their final concentration 0.05 molecular, the following is noted. After ten minutes immersion it is plainly evident that some of the salts are accelerating the effect of the acid in producing the development of the cloudiness, while others are inhibiting it. In an hour the differences are very marked. The sulphocyanate, iodide, bromide, and nitrate all increase the cloudiness, the first named being the most powerful in this respect. Then comes the pure acid. Following this comes the chloride, the acetate, the tartrate, and the citrate. After three to six hours of immersion the differences are still more striking. In the solutions containing the first-mentioned salts the tissues are "boiled" in appearance. In the pure acid the grayness is well marked. The tissues in the solutions containing the chloride and the acetate lag somewhat behind the pure acid. In the tartrate a faint film is only just visible over the surfaces of the organs. The sections in the solutions containing the citrate look perfectly normal. In fact, in the two last-named solutions the organs retain an almost normal appearance for two to three days.

Similar results are obtainable by using sodium or ammonium salts in place of the potassium salts, or lactic, formic, or nitric acid in place of the hydrochloric, except that in the latter case the absolute rates at which any degree of cloudiness is obtained is not quite the same as in hydrochloric acid.

(*d*) Various salts accelerate or retard the development of a cloudiness in sections of kidney placed in their *pure* solutions, in just the same way as they accelerate or retard the development of a cloudiness if an acid is added at the same time, only the rate of development and the absolute intensity of the cloudiness attained is less in the pure salt solutions than in mixtures of these with any acid. In all salt solutions the kidney slices swell less than in pure water. These findings are to be interpreted by noting that the excised tissues become acid, so that the tissues placed in the pure salt solutions are really in the same state as the tissues described in the preceding paragraph — the tissues are really in an acid solution plus certain salts — only the concentration of acid is lower in this case than in the previously described experiments.

(*e*) Alkalies do not produce a cloudiness of kidney parenchyma in any concentration. Sodium, potassium, ammonium, and calcium hydroxides were employed in concentrations up to 0.03 normal. The superficial layers of the tissue slices "dissolve" in the hydroxides, covering the tissues with a clear gluey mass. After two or three days the tissues lose their bright normal color, but the grayness assumed is only slight. The slices of kidney swell just as they do in acid solutions.

(*f*) The addition of any salt to the solution of an alkali does not lead to any cloudiness of the tissues, though it markedly reduces the tendency of the superficial layers of the tissues to go into "solution," and the swelling of the tissue fragments as a whole. I have tried the chlorides, bromides, iodides, nitrates, sulphates, sulphocyanates, acetates, tartrates, and citrates of sodium, potassium, and ammonium in conjunction with the hydroxides of sodium, potassium, and ammonium without effect. I have also tried a few strontium and barium salts with these hydroxides and calcium hydroxide, employing all in such low concentrations as to prevent the formation of precipitates, but I got no cloudiness of the immersed tissues.

(*g*) The macroscopic changes observed in the kidney when this is immersed in water, various acids, or alkalies, in salt solutions or these in combination, show a series of interesting parallels microscopically.

A perfectly fresh scraping from the kidney shows the cells to possess a fairly clear protoplasm in which lie but few granules. Even after the kidney cells have been kept for twenty-four hours (simply in their own moisture, and protected against evaporation by being covered) they show no change from this appearance. But as soon as water touches the cells, especially if the organ has been kept for twenty-four hours, or if they are placed in any very dilute acid, a grayish film is seen to develop macroscopically, and microscopically the cells are now found thickly studded with granules. This is the typical histological picture of the cloudy swelling described in our textbooks of pathology. If now, while such cells are being observed, a little caustic soda is allowed to run under the cover slip, the cells as a whole are seen to swell, the granules to become fainter, then fewer, and finally to disappear entirely, and if enough alkali is added the whole goes into homogeneous "solution."

The granules can also be made to disappear by the addition of more acid; they form, for example, in very dilute acid, and disappear again if the concentration of this same acid is raised. Most interesting is the fact that this granular appearance can be made to come a second time by still further increasing the concentration of the acid. Acetic acid will not do this, but nitric acid will do it promptly. If strong nitric acid is used this second appearance of the granules is only a temporary affair, for they again disappear as the whole tissue goes into "solution." With the second appearance of the granules the cells undergo a marked shrinkage from the more swollen state attained previously, but this shrinkage, like the second appearance of the granules, is also only temporary, and the cell undergoes a final enormous swelling before being "dissolved."

§ 3.

How now are we to interpret these various findings, and what light do they bring us regarding the cause and the essential nature of those changes of like character, which we observe in the kidney in nephritis and which lead to the increase in its size and to the change in its color? Our first attention must be dedicated to the matter of the *increase in the size of the cells.*

H. J. Hamburger recognized very clearly that the fundamental cause for the increase in the size of the cells affected with cloudy swelling lies in the production of acid in them. As we have already learned, evidences of *an abnormal production and accumulation of acid in the kidney occurs in every case of nephritis, and so we may make this condition, which we have already made responsible for the albuminuria, responsible for this increase in the size of the kidney also.* But how does an abnormal acid content manage to bring about the increased water absorption which leads to the increase in the size of the cells (and so of the kidney as a whole) in nephritis? *Hamburger* answered this question by attributing an indirect effect to the acid, whereby this was assumed to increase the osmotic concentration within the cells. The enlargement of the cells in "cloudy swelling" represents an œdema of the affected cells, and this is most easily accounted for on the basis of the colloidal constitution of living matter.[1] The serious objections that can be lodged against the widely-accepted belief that cells represent osmotic systems cannot be raised against the view that the (lyophilic or emulsion) colloids of the tissues and their state determine the quantity of water absorbed by a cell. As is well known, the amount of water that such colloids (as represented by gelatine, fibrin, and serum albumin, for example) will absorb is enormously increased if any acid is present. This fact receives incidental illustration in Fig. 1. On this basis, *it is easy to parallel the absorption of water, and so the enlargement of the cells and the kidney as a whole, when affected with nephritis, with the increased amount of water absorbed, say by a gelatine cube or some fibrin particles, when instead of being placed in water they are placed in a dilute acid of some kind.* In the case of gelatine and fibrin, and similarly in the case of the experiments on excised kidneys, the source of the water for the increased swelling is to be found in the solutions surrounding these colloidal structures; in the case of the nephritic kidney, in the blood and lymph streams passing through the organ.

There is, within certain limits, an increase in the amount of the swelling of such emulsion colloids as gelatine or fibrin with every increase in the concentration of the acid surrounding them. On this basis we can understand the increase in the swelling of the kidney cells with every increase in concentration of the acid up to a certain point. When a certain optimal concentration of the acid is exceeded, the colloid swells less than in weaker solutions (see Fig. 1). This furnishes a ready interpretation of the finding detailed above, that on substituting nitric acid for a weaker solution of acetic acid, kidney and liver cells are seen to shrink. Incidentally, it is worth while to emphasize that in the great rapidity with which such cells will give up and take up water, in changing from a medium of one concentration to another having a lower or a higher one, lies a powerful argument against the osmotic pressure idea of water absorption in cells. I have seen these cells pass from the swollen state, in a weak acetic acid solution, to the greatly shrunken state induced by nitric acid, and through a second swollen state into "solution" in less than two seconds. Equalizations of osmotic differences either through a movement of solvent, or of dissolved substance, do not occur with such velocity.

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[1] See *Martin H. Fischer:* Œdema, 85, New York, 1910.

We may now turn to a consideration of *the changes in the color of the kidney in nephritis*, and see how these become interpretable on the basis of the fact that in this condition an abnormal amount of acid is present in the kidney.

The statements made above regarding the means by which a cloudiness can be produced in the parenchymatous cells of the kidney, or the rate of development, or the intensity of such a cloudiness be increased or decreased, have all of them parallels in the ways and means by which protein may be precipitated from one of its "solutions," or such a precipitation be hastened or retarded. *The development of a cloudiness in the kidney cells follows most closely the solution and precipitation of such a colloid as casein.*[1]

Casein[2] is insoluble in water. It is soluble in dilute hydroxides, in which state it is electro-negative. It is in this state that we find the body proteins normally, as *Wolfgang Pauli*[1] has shown. When a dilute acid is added to such an electro-negative protein, let us say to a solution of casein in any hydroxide, a precipitate of the casein is thrown down. A similar precipitation of an electro-negative colloid occurs when our sections of kidney are immersed in any dilute acid. The development of a cloudiness in tissues immersed in water is also to be regarded as a precipitation through a dilute acid, only in this case the tissues themselves produce the acid. Similar conditions hold in nephritis, when, in consequence of the abnormal acid content of the kidney, some of the protein constituents of the cells composing this organ are precipitated. As we have already found this same acid to be responsible for an increased affinity of the tissue colloids for water, it is easy to see how from the two there results, when water is available, the picture we designate "cloudy swelling."

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[1] This term is used in *Hammarsten's* sense and corresponds therefore with the caseinogen of *Halliburton*.

[2] For a discussion of the general properties of casein see *O. Hammarsten:* Physiological Chemistry, Translated by *Mandel*, New York; *E. Laqueur*

But our analogy goes further than this. If we continue to add acid to the reaction mixture in which our casein was last precipitated, we find that with an increase in the concentration of the acid the casein goes back into solution. This is what we observe in the kidney cells when we note the cloudiness produced in a weak solution of any acid, or that found in the nephritic kidney on autopsy, to disappear on applying a stronger solution of the acid (say acetic acid) to the kidney. This macroscopic change has its parallel in the microscopic disappearance of existing granules in a cell, the seat of a cloudy swelling (found either post mortem or induced artificially), when acetic acid is run under the cover slip. But the casein thus redissolved in

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and *O. Sackur:* Hofmeister's Beiträge, **3**, 193 (1903); *W. A. Osborne:* Jour. Physiol. **27**, 398 (1901); *T. B. Robertson:* Jour. Biol. Chem., **2**, 317 (1907); *L. L. van Slyke* and *E. B. Hart:* Am. Chem. Jour., **33**, 461 (1905).

[1] *Wolfgang Pauli:* Naturwissensch. Rundschau, **21**, 3 (1906).

such an acid as acetic acid can be precipitated a second time if strong nitric (or hydrochloric or sulphuric) acid is allowed to flow into the test tube. If the protein is not present in excessive amounts, this second precipitate also disappears: we say it goes into solution in the excess of the nitric acid. It is not difficult to see that this is entirely analogous to the reappearance of granules in the kidney cells, with subsequent total solution of the affected cells, on the addition of nitric acid for example, to cells in which a previous set of granules has been made to disappear by the addition of acetic acid.

Equinormal solutions of different acids are not equally effective in producing a precipitation of casein, neither are they equally effective in producing the cloudiness of cloudy swelling. In low concentrations certain salts favor the precipitation of casein in dilute acids while others hinder this. The sulphocyanates and iodides quickly precipitate casein from an acid solution in heavy curds. Equimolecular solutions of the bromides, nitrates, and chlorides produce only an opalescence, while in citrates the casein remains in solution. When arranged according to the intensity with which these anions favor the development of a cloudiness in the kidney the order is the same. Various kations, in the dilute solutions in which they have to be used to prevent their precipitation as hydroxides, do not influence the precipitation of casein. Neither do they affect the development of cell cloudiness.

Kidney cells also follow the behavior of casein toward alkalies. All the alkalies make casein go into solution and, similarly, the alkalies do not produce any clouding in kidney cells.[1] Casein is not precipitated in alkaline solution by the addition of any of the ordinary salts. Neither is a cloudiness produced when any salts are added to slices of liver or kidney immersed in a dilute alkali.

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[1] The slight grayness developed by slices of kidney, kept for several days in a dilute alkali, has its parallel in the turbidness which we find developed in alkaline solutions of casein, when these are kept for longer periods of time.

Point for point the analogy between the precipitation of casein and the artificial development of a cloudiness in kidney cells seems therefore to be complete, and since there exists no discoverable difference between the changes thus artificially induced in excised kidneys and those which nature produces for us in this same organ in nephritis, nor yet in the conditions leading to these changes in either case, we would seem to be justified in considering all these changes as in essence the same, and as caused fundamentally by the same circumstances.

As this process of cloudy swelling represents a series of changes in the state of the cell colloids, it is clear that the employment of any methods in its study — such as fixing agents and various stains — which in themselves are capable of producing changes in the state of cell colloids, should be excluded. Nevertheless, to meet the possible objection that what has been described in these pages as cloudy swelling might really not be identical with this change as observed on the autopsy table, our pathologist, *Paul G. Woolley*, generously offered to examine by approved histological methods the tissues in which I had produced cloudy swelling artificially. He reports that the pictures obtained are identical with the most extreme grades of cloudy swelling that are encountered pathologically.

In concluding these paragraphs we have to answer the final question of *the relation of the swelling of the kidney cells to the clouding in them.* On the basis of the fundamental work of *Wolfgang Pauli*[1] and his coworkers, *Hans Han-*

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[1] *Wo. Pauli:* Kolloid Zeitschr., **7**, 241 (1910); *Pauli* and *H. Handovsky:* Biochem. Zeitschr., **18**, 340 (1909) **24**, 239 (1910); *H. Handovsky:* Kolloid Zeitschr., **7**, 183, 267 (1910); Fortschritte in der Kolloidchemie der Eiweisskörper, Dresden, 1911; *Karl Schorr:* Cited by *Pauli* and *Handovsky.*

dovsky and *Karl Schorr,* this is easily done. As these investigators have shown, the swelling and solution of a protein colloid (its hydration) and the loss of water and precipitation of this same colloid (its dehydration) represent antagonistic processes and are therefore mutually exclusive. It follows from this that the swelling of the cells in a parenchymatous nephritis, and the development of a cloudiness in them, can impossibly involve the same colloid, — in other words, at least two must be involved. The conditions which permit the one of these to imbibe water and so lead to an increase in the size of the cell are of such a character as to lead to the precipitation of another, and so to the cloudiness. *Wolfgang Pauli* kindly advised me to test out this idea in a model made by pouring a solution of casein (prepared by saturating sodium hydroxide with casein) into a concentrated, carefully-washed gelatine (20 per cent) and allowing the whole to stiffen. When plates are cut from such a mixture they swell (absorption of water by the gelatine) and become cloudy (precipitation of casein) under the same conditions (presence of acids and various salts) as were found above to lead to a "cloudy swelling" in slices of kidney.

4. The Bleeding into and from the Kidney in Nephritis (Hæmorrhage by Diapedesis).

The blood that appears in the urine in some cases of nephritis may have a purely traumatic origin; in larger part, however, pathologists hold that it gets from the capillaries into the urine by diapedesis. Through diapedesis are also explained the hæmorrhages into the kidney substance itself. As such bleeding does not occur from the normal kidney, we become interested in its mechanism, and it becomes a part of our problem to discover why in nephritis such a process of diapedesis, which occurs also in other pathological states, should be especially prone to appear.

We still lack a satisfactory explanation of the mechanism of diapedesis. Our present teachings continue to partake of the views of *von Recklinghausen* and *Julius Arnold*, who held that holes (so-called stomata) exist in the capillaries, and that through these the red blood corpuscles escape in conditions associated with a bleeding by diapedesis. But such a condition, as *Julius Cohnheim* pointed out years ago, is grossly incorrect, for what escapes from the blood in hæmorrhage by diapedesis is not the whole blood, but only the red blood corpuscles, and it is inconceivable how holes which would permit the passage of the cellular elements of the blood through them should hold back the liquid portion of the blood. *Cohnheim* believed diapedesis to be dependent upon changes in the blood vessel walls whereby these became abnormally permeable, after which he held the blood pressure to be able to force the red blood corpuscles through them. How such an abnormal permeability was brought about he declared himself unable to explain.

Hæmorrhage by diapedesis, while discussed by us because present in some forms of nephritis, is really, of course, a widely distributed pathological phenomenon. As is familiarly known, it occurs in any well-marked passive congestion, produced, for example, by ligation of the veins of any of the parenchymatous organs, of the mesenteric veins, or of those coming from the leg or the ear of a rabbit or dog. But it occurs also after ligation of the arterial blood supply to a part, and I have observed it in the entire absence of any circulation in the legs of frogs so ligated as to close both arteries and veins, and kept in a little water. Hæmorrhage by diapedesis occurs also in conjunction with the acuter forms of inflammation no matter how induced.

It is clear from these few remarks that blood pressure, which might at first sight be thought to be of some importance in squeezing the red blood corpuscles out of the blood vessels into the surrounding tissues, cannot be of great importance in this regard, for diapedesis occurs in conditions associated with a decrease in the blood pressure, or, as just pointed out, even in its entire absence. What is present in all the conditions noted is such a disturbance in the circulation as to lead to a state of lack of oxygen in the tissues, and, we have to repeat, an abnormal production and accumulation of acids in the affected regions. And this is what we have in the kidney in nephritis. But how does this now lead to the diapedesis? The answer is not hard to find.

We have already called attention to the well-known fact that the cells of the living organism represent in the main a mixture of several so-called lyophilic or emulsion colloids. Under normal circumstances in the body these are in a swollen state that is similar to that assumed by fibrin or gelatine when placed in water. If a little acid is introduced into such a colloid the absorption of water by it is enormously increased, and as we have already pointed out before, this is what happens when acid is introduced into the kidney (or into the tissues of the other parenchymatous organs, the intestine, the leg, or the ear), in other words, an "œdema" develops. But this increased absorption of water makes the tissue *softer* (or to put it more technically, its internal friction is decreased and its surface tension is changed) and now the red blood corpuscle which lies in contact with its surface is no longer held out by the surface layer of the tissue colloids (the blood vessel wall) but penetrates this — is really "swallowed" by the tissue. The increased fluidity of the kidney tissues, after these have been treated with a little acid in the presence of water, is readily observable under the microscope. The cells can be pushed about and molded on slight pressure in a most striking way.

What makes the red blood corpuscle move through the tissues are inequalities in the stresses present in the tissue colloids. By a process, the reverse of that described, the tissue which has once swallowed a red blood corpuscle may again get rid of it, though in practice such a result is hardly to be expected, for after a softened tissue that has swallowed some red blood corpuscles has a more normal circulation once more restored to it, it is likely to lose its excess of acid, and so its water, so rapidly that the red blood corpuscles remain behind entangled in the tissues. As a matter of fact we know that the red blood corpuscles that have escaped into the tissues are usually absorbed indirectly, after they have disintegrated.

What we have said here regarding the red blood corpuscles holds of course also for the *white blood corpuscles* only these possess in addition independent powers of movement which are *lacking* to the red blood corpuscles.[1] More strictly in the class with the red blood corpuscles belong *the bacteria* which we know may reach the kidney from any part of the body and pass through the kidney substance out into the urine.

Briefly formulated, the problem of how the red blood corpuscles in nephritis pass into the tissues of the kidney or

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[1] In the discussion of the migration of white blood corpuscles in inflammation (chemotaxis) most emphasis is always laid upon the changes that the white blood corpuscles themselves are believed to suffer (for example, changes in surface tension), which result in their movement toward the inflammatory center. This is only half the problem. The changes in the tissues themselves (changes in viscosity, for example), produced through the action of the excitant of the inflammation, also play a rôle.

through these out into the urine, or the problem of how white blood corpuscles or bacteria do this comes to be the problem of how one colloidal body may pass through another, and of the laws that govern such a passage. No holes are necessary in order that one colloid may pass through another, and such a passage is accomplished without one colloid losing its identity in the other or leaving behind it any evidence of its passage.

The matter can be prettily illustrated by letting a mercury drop or solid metals (iron fragments or shot, or these covered with colloidal material as agar-agar or collodion), under the influence of gravity, move in all directions through a solidified gelatine. The mercury is particularly suitable, for, while not a colloid, it has the "liquid" character possessed by the red and white corpuscles. In the body the migration of the blood corpuscles (or metal fragments, etc.) does not of course occur under the influence of gravity, but in consequence of inequalities in the pressure exerted upon the surface of these elements, occasioned through inequalities in the stresses present in the tissues (brought about in turn through local changes in the water content of the lyophilic colloids comprising the tissues). And as the question of whether a mercury drop will enter a solidified gelatine, and the rate at which it will move about in this are matters that have to do with the surface tension relationships that exist between the mercury and the gelatine, and the viscosity of the gelatine (in its turn, affected by concentration, temperature, acids, bases, and salts), so these same factors play a rôle in diapedesis as observed in the living organism.

In Fig. 15 is shown how a mercury drop is unable to penetrate a stiffened gelatine (3 per cent) at room temperature. It may be rolled about on the surface of the gelatine without entering it. If now this experiment is repeated at the same temperature, with a stiffened gelatine of a somewhat lower concentration, the mercury drop enters it and falls slowly to the bottom (Fig. 16, *a*, *b*, *c*). By turning the tube about (Fig. 17), the mercury drop will move in all directions through the stiff gelatine in which of course no holes exist, and in which none remain after the mercury has passed.[1]

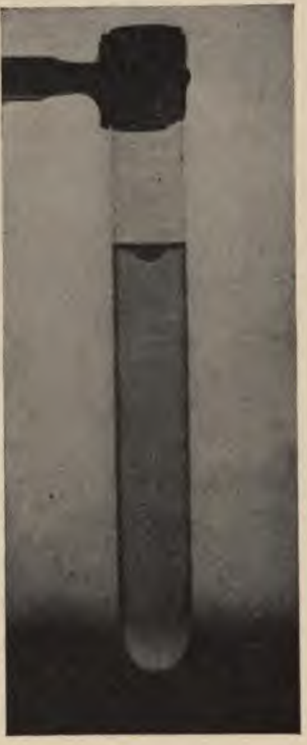

FIG. 15.

The essential change in the gelatine, which makes such penetrability possible in this experiment, was induced through regulation of the concentration. A similar change can be induced by raising the temperature somewhat (not to the point of melting the gelatine, of course) or, *in the presence of water*, by adding a little acid. This approximates most closely the change that occurs in the body when in passive congestion, for example, a diapedesis into the œdematous tissues is noted. What happens under such circumstances can also be mimicked with some gelatine cubes and a few mercury drops. If two gelatine cubes are placed, the one in water, the other in a dilute acid, the one in acid undergoes a swelling, which after a time reaches a stage at which it will readily admit of the passage of a mercury drop, while the control in water will not do so.

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[1] It is this property of colloids which explains easily why small wounds made in the living animal close immediately. The property of colloids, which gives them such great interest biologically, is the fact that they combine in one the properties of liquids (surface tension, viscosity, diffusion of dissolved particles) with the properties of solids (maintenance of form).

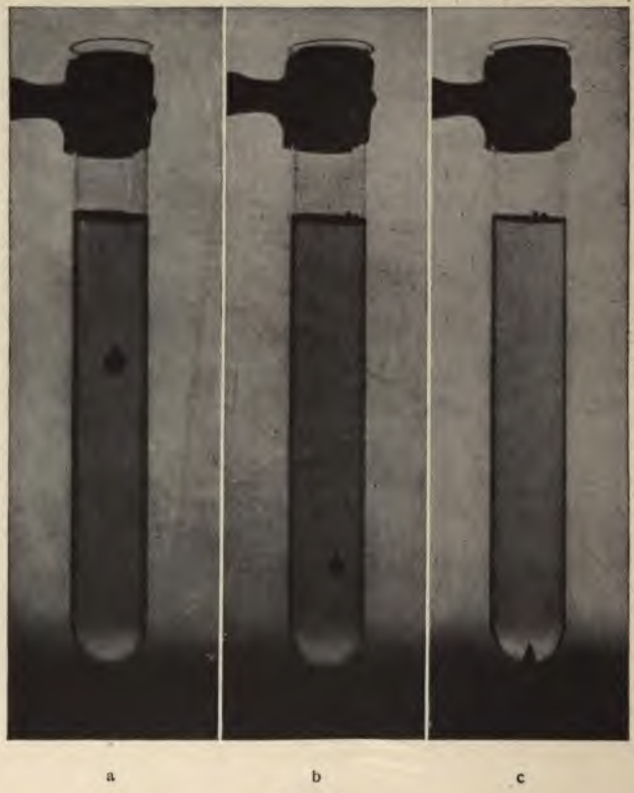


FIG. 16.

5. On the Origin and the Different Types of Tube Casts.

In this section we will discuss how the abnormal acid content of the kidney in nephritis leads to the formation of casts. At the same time we will learn how the various types of casts that are discovered in the urine in nephritis bear a simple relationship to each other; how, in fact, it is possible to convert one type of cast into another, and back again if we so choose, under the conditions found in the kidney and in the urine in nephritis.

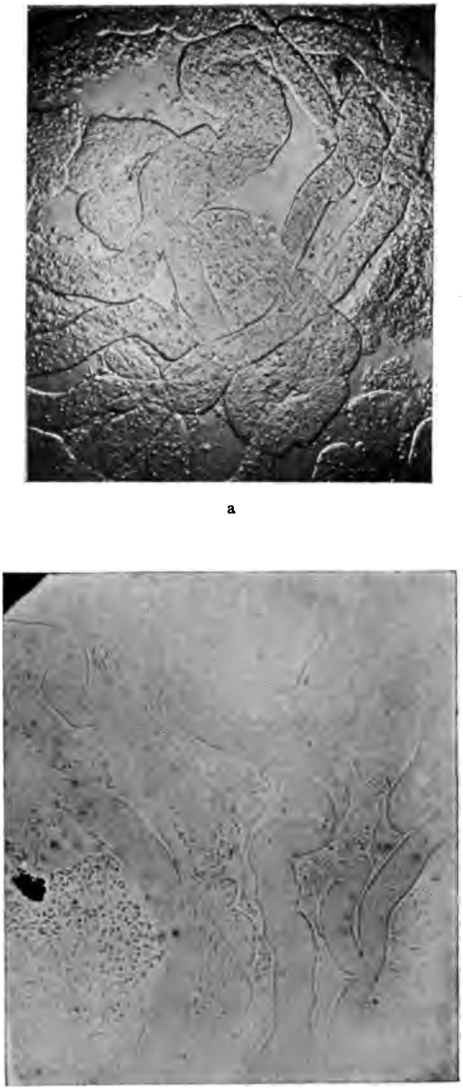
FIG. 17.

What must be the effect of the abnormal production or accumulation of acid in the kidney, so far as this problem of casts is concerned, may be determined in any one or all of several ways. We may simply leave the normal kidney, freshly removed from the body, to itself, protect it against evaporation, and study the effects of the post mortem development of acid in it. Or, we may slice the kidney into several pieces and place them in water, or, finally, we may place such slices directly into slightly acidified water. The kidneys of guinea pigs and rabbits furnish excellent material and it is on these that the following observations were made.

When we take a *fresh kidney* that has been cut across and squeeze it gently, we only see a little blood ooze from the blood vessels. If we scrape the surface and put a little of the scrapings on a slide, we find little more than some red blood corpuscles mixed in with a little granular material. We find that it is difficult to obtain any kidney parenchyma cells, — they do not separate easily from their attachments. The same kidney, preserved for several days, presents a somewhat different appearance. The surface may not be quite so glistening when cut, and on squeezing the organ turbid points arise over the surface of the kidney which, when examined microscopically, are seen to be made up of epithelial cells which have loosened from the kidney tubules. These may be single, or joined together in groups, and with them are again found the red blood cells and the granular detritus that was observed in a scraping from the perfectly fresh kidney.

A somewhat different picture is presented by the sections of kidney that are placed in water. These tissues become gray more quickly than the tissues that do not come in contact with water, and develop an opaque appearance. The normal kidney markings become gradually more and more obscured, and the tissues as a whole are seen to swell somewhat. The whole makes up the typical picture of that which the pathologists call cloudy swelling, and the nature of which we discussed in a foregoing section. A scraping from the surface of such a gray kidney shows a large number of free epithelial cells, which one has no difficulty in recognizing as coming from glomerular tufts and from the uriniferous tubules. In making the scraping one notices, moreover, that while vigorous scraping yielded little or nothing when applied to the healthy kidney, it is no trick at all to get an abundant amount of material from the surface of a kidney that has lain in water for a day or two. One notices, moreover, that the numerous epithelial cells are swollen and studded with granules. But beside the individual epithelial cells one notices groups of these, and then casts with rounded ends of whole tubes. One has no difficulty in recognizing these as duplicates of the epithelial casts found in the urine in certain types of nephritis.

But the most striking picture is that presented by the sections of kidney that we have thrown into a very weak acid of some kind. In this the cloudy swelling of the slices of kidneys already described occurs very rapidly. *A gentle*



a

b

FIG. 18.

scraping from the surface of a kidney slice, treated with such a dilute acid (0.002 normal lactic, for example), *shows in several hours after immersion a granular detritus, separate epithelial cells, groups of epithelial cells, and casts of various kinds* (Fig. 18, *a* and *b*). *When the kidney is simply gently squeezed and its surface touched to a slide, and this is then examined microscopically, one cannot escape the impression that he is examining a centrifuged urinary specimen from a case of acute nephritis. The epithelial cells, the epithelial casts, the granular casts are all there. One misses only the hyaline cast, but this can be promptly obtained by simply adding a little stronger acid to our specimen under the microscope, when our granular casts are seen to lose their granules, swell somewhat more decidedly, and become difficultly visible.* Scattered nuclei may stick to the casts, but if enough acid is added, these too go, so that only the greatly swollen, entirely hyaline "cylindroids" of some authors remain. Or, we can assure ourselves of a generous yield of hyaline casts and cylindroids from the start if we simply increase the acid concentration into which we drop our kidney slices, or prolong their residence in the solution.

We can convert the granular casts into hyaline ones quite as easily through the addition of an *alkali* as through the addition of an acid, and if the kidney slices are from the first dropped into a dilute alkali, only hyaline casts are obtained. The hyaline casts produced through the acids can be converted back into granular casts, if we wish, by simply running a little salt under the cover slip. A sulphocyanate is particularly good for this purpose, but if we wish to use a salt that is more "physiological" in nature, sodium nitrate or sodium chloride will do. The hyaline casts produced through alkalies can also be converted into granular ones, though to accomplish this they must be treated with an equinormal acid. Why all these transformations are possible is, of course, readily intelligible when the experiments on cloudy swelling as detailed in the previous sections are recalled to mind.

In Fig. 19 is shown the appearance of a gentle scraping taken from a slice of kidney that had lain in water for several hours. A granular cell detritus and isolated casts characterize such a specimen. Nuclear fragments are prominent, and the epithelial cells may in places still be made out. The cells are granular. In Fig. 20, *a*, is shown a scraping similarly prepared from a slice of kidney that had lain in a 0.005 normal acetic acid for three hours. The cast formation (falling apart of the kidney) is a far more prominent feature. In the cast occupying the central point in the photomicrograph remnants of an epithelial structure are still present. In the casts lying above this all evidences of nuclear structure have disappeared. They are filled

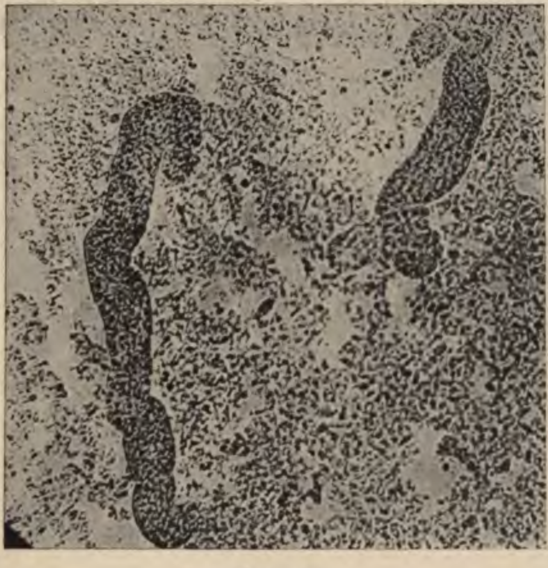


FIG. 19.

with fine granules. When these casts were treated with a stronger solution of acetic acid they became hyaline, as shown in Fig. 20, *b*.

It is clear therefore that under the influence of a little acid the kidney drops apart into its morphological elements. While these are firmly cemented together in the healthy kidney (as witness the attempt to obtain them by scraping the surface of the kidney with a knife), they are separated with the greatest ease after the kidney has lain in acid for a while. The answer as to why the kidney falls apart as it does under the influence of acid it is needless to discuss, but the view that some of the (colloidal) "cement substance" is easily "soluble" or is easily "digested" in weak acids at once suggests itself. Such a view finds support in our previous considerations of albuminuria and the fact, easily observed in these experiments, that the solutions in

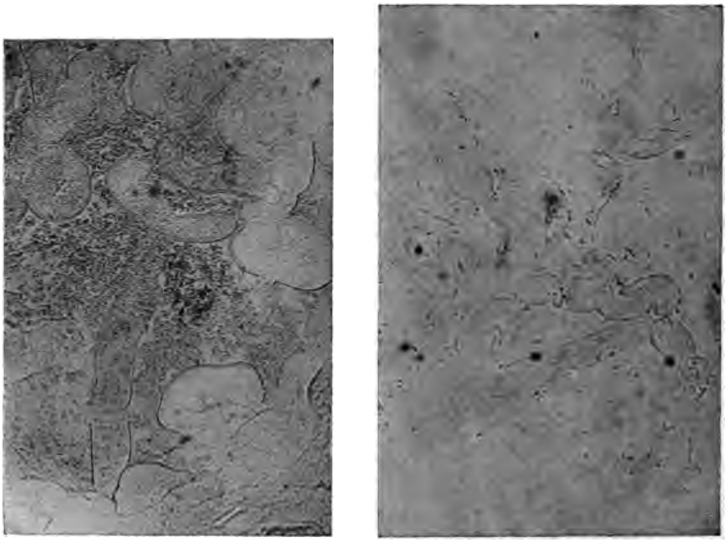

a b

FIG. 20.

which the kidney slices lie come to contain with time progressively larger amounts of albumin. That some constituents of the kidney (or of any other organ) are more readily soluble in an acid than are others, is clearly enough evident under the microscope. The nuclei of the cells still retain their outlines, for example, in concentrations of acid in which the protoplasm generally has become entirely hyaline. The action of the acid could be aided and abetted, of course, by various enzymes.

What is important to us, from the standpoint of the theory of nephritis, is *the way in which the kidney falls apart. The epithelial cells tend to stick together while they separate in mass from their supporting membrane. This marks the origin of the urinary cast* which, in clinical cases, is washed down into the bladder by the force of the secreted urine.

These simple facts regarding the origin of casts, and the conditions under which the one type may be converted into another, are not without some clinical significance. In treatises on medicine and in works on clinical diagnosis much has been said, not only regarding the significance of the appearance of casts in the urine, but of the significance of the different kinds of casts. It seems to me that the experiments that have just been detailed urge upon one the necessity of caution in drawing too sweeping conclusions from such data. So far as mere numbers of casts are concerned it requires no special emphasis to realize that great numbers of casts present in the urine at one time, while indicative of a more extensive involvement of the kidney parenchyma, may not be as significant as a lesser number present over longer periods of time. The aggregate destruction may in the latter case, of course, be much greater than in the former (a condition further modified in the living organism by the rate and quantity of the regeneration occurring in the kidney).

In judging of the meaning of the character of the cast, whether epithelial, granular, or hyaline, one must be exceedingly careful. We have seen, first of all, that the epithelial cast is readily convertible into either the granular or the hyaline, depending only upon how much acid is present and the length of time that it is allowed to act; and the hyaline, we have seen, can be reconverted into the granular. The thought might suggest itself that we use the nature of the cast as an index of the degree of the acid concentration in the kidney and so as a measure of the intensity of the nephritis. But this may not be done, for we know from autopsy findings that a nephritis need not affect all the parts of a kidney equally, or at the same time, and the urine represents a mixed product of the whole kidney. Moreover, the urine itself varies so in composition under different (physiological) circumstances that it may alter the character of the cast in its passage through the ureter and bladder, no matter what its nature when it left the kidney. A highly acid urine would on the whole tend to yield granular or, if sufficiently high, hyaline casts. An alkaline urine would tend to yield only hyaline casts. On the other hand, the salts of the urine would tend to counteract the acid and make the casts not only smaller (loss of water by the colloid) but more granular (precipitation of the colloid). One can easily satisfy himself of these facts by providing himself with casts from a clinical case of acute nephritis, or from such kidneys as I have described, and examining them under the microscope, while a little acid, or this in conjunction with various salts, is allowed to run under the cover slips of the preparations.

In concluding this section it is well to revert for a moment to the question of albuminuria. It is possible to test the idea that albuminuria results from a " solution " of the proteins of the kidney under the influence of an acid in conjunction with these experiments on the formation of casts. If we take a perfectly fresh kidney from either a rabbit or a guinea pig, cut it into several slices, and then wash the pieces a few times in water or a "physiological" 0.9 per cent NaCl solution, so as to get rid of the blood in the kidney, we find thereafter that the wash water gives little or no reaction for albumin. But if we permit the pieces of kidney to lie in the wash water until next day, we have no difficulty in getting the albumin reaction. Still more rapidly do we get this reaction if we immerse the washed slices of kidney from the start in a weak acid solution. Then we get the reaction for albumin promptly. If we pipette off the sediment found about the kidney pieces and examine this under the microscope, we find at the same time various kinds of casts. But the albumin is not simply due to these, for we get a marked albumin reaction after carefully filtering the solution about the kidney pieces.

III. THE DISTURBANCES IN SECRETION IN NEPHRITIS.

1. General Considerations.

The changes observed in the secretion of urine in any case of nephritis fall into two groups: the changes in the amount secreted in any unit of time, and the changes in the quantitative composition of the urine. In all except the so-called chronic interstitial types of nephritis the secretion of water is diminished. In the chronic interstitial types it is said to be increased. So far as the secretion of dissolved substances in nephritis is concerned, it is generally accepted that (diet duly considered!) there exists not only a diminution in the total amount of dissolved substances eliminated, but variations in the proportion of the dissolved substances eliminated when compared with each other and regarded in the light of the way in which these same substances are eliminated during health. What happens here is very interesting. We find that certain substances may be eliminated as well by the diseased kidney as by the normal. Certain other substances are eliminated in much smaller amounts than is normal, so small, in fact, that it is often said not at all. Experiments and observations to indicate that a nephritic kidney may secrete yet other substances even *better* than a normal kidney are not on record so far as I know. Quantity of urine duly considered, such a thing is theoretically not impossible.

Before we can to advantage consider the secretion of water and of dissolved substances by the kidney, we shall first have to return to a further consideration of the position occupied by chronic interstitial nephritis in our general classification of the nephritides. As is generally known, the secretion of water by the patient with chronic interstitial nephritis is not diminished as in all the parenchymatous forms, it is normal in amount, or, as the majority of clinicians and pathologists are wont to say, it is increased in amount. In discussing this problem of why in chronic interstitial nephritis we do not have the diminution in output of water observed in the parenchymatous forms, we shall at the same time touch upon the questions of the increased blood pressure and the heart hypertrophy observed in the chronic interstitial forms and absent from the parenchymatous forms.

2. Further Remarks on the Relation of Chronic Interstitial Nephritis to the Parenchymatous Types.

1. To the claim that in chronic interstitial nephritis the amount of urine secreted is increased, serious objection must be made. It is better to simply say that the output is normal. Urinary secretion is normal if (with due

regard to loss of water through skin, lungs, and intestinal tract) all the water consumed by an individual is excreted again, as urine, — that is to say, none is retained (œdema) and not more than has been consumed is excreted (abnormal loss). If a man consumes only a liter of water a day and secretes a liter of urine (skin, etc., being ignored) his urinary secretion is normal, and if he consumes twenty liters and secretes twenty it is normal. We may differ as to which of these amounts, if either, we consider as normal (better optimal) from the standpoint of *consumption*, but so far as secretion is concerned, both are normal. And for this reason I would insist that the patient with chronic interstitial nephritis, who happens to consume in response to his tastes three liters of water and so secretes three liters of urine (skin, etc., again ignored) has not an increased urinary output, but a normal one. *So far as water output is concerned the patient with chronic interstitial nephritis is simply not nephritic.*

But he is not a nephritic from other standpoints either. He has not the œdema of the parenchymatous types. He has not the evidence of excessive acidity in his urine, as already pointed out in discussing *R. Höber's* analyses of the urine in nephritis. Neither has he the albumin, the casts, or the blood that are found in parenchymatous nephritis. We can carry this still further. If a patient without these signs and symptoms dies, and on the autopsy table we find the small kidneys (" small red kidneys ") that we diagnose anatomically as chronic interstitial nephritis, then the parenchyma cells of the kidney — the only parts of the kidney that are concerned with its physiological function — are also found looking normal. The small, red kidneys are, except for size, normal kidneys. *So far, chronic interstitial nephritis is not nephritis at all, it is an atrophy of the kidney.* This is the typical picture of the man who lives for months or years without symptoms of kidney disease, and in whom we diagnose chronic interstitial nephritis post mortem.

Let us now consider the man who has been less fortunate in this regard, the patient in whom we have before death diagnosed a chronic interstitial nephritis because we have found a few casts, occasional traces of albumin, and let us add, an arteriosclerosis, a hypertrophy of the left ventricle, and a high blood pressure. To drag in a symptom often referred to in these cases let us suppose that he tells us that he has to rise one or more times nightly to urinate. The more pronounced the albuminuria, and the more steady the appearance of casts, the more certain are we of finding, on autopsy, not the small, red kidney, but the swelled (small) *gray* kidney! In other words we get the (physiological) characteristics of parenchymatous nephritis added to what (morphologically) we call chronic interstitial nephritis. And when we study these cases carefully we find that, as the albuminuria and the formation of casts increase, the ("increased") urinary output also falls, and along with it we are likely to note the first evidences of an œdema. Symptomless and signless, interstitial nephritis is therefore essentially an atrophy of the kidney, and the individual so affected behaves and dies like the animal that has had its kidney substance removed by successive operations down to the physiological minimum. Chronic interstitial nephritis with casts, albumin, etc., is the mixed picture resulting from a (morphologically) chronic interstitial nephritis plus a parenchymatous nephritis.

All that now remains unexplained in this picture of chronic interstitial nephritis is the arteriosclerosis, the hypertrophy of the heart, the increased blood pressure, and the incident that the urinary secretion is of such a character that the patient is disturbed at night. Let us take these up seriatim, and in our discussion let us not be misled into that pitfall which would make of a sick animal a something for which the established laws of physiology are no longer valid.

2. The bearing of *arteriosclerosis* upon kidney disease has to be considered from two viewpoints. Is the arteriosclerosis responsible for the kidney disease, or vice versa? The kidney associated with arteriosclerosis is the contracted kidney, the chronic interstitial type. Such a kidney shows as a rule the greatest variety of morphological changes. While certain regions are entirely normal in appearance, other patches show characteristic "degenerative" changes, as evidenced by the presence of cells that are swollen and granular, or perhaps have lost their nuclei and are disintegrated (*localized* parenchymatous nephritis). To take the place of the dead cells we may find new parenchyma cells forming, or there may be found evidences of connective tissue proliferation indicating the ultimate formation of a scar.[1]

This patchy appearance, resulting from a mixture of normal, degenerating and regenerating cellular elements in the kidney, stands in marked contrast to the uniformity of appearance presented by a kidney that has been poisoned, say, with the toxines of an acute infectious disease. Here, in a certain sense, all parts of the kidney are affected and to about the same degree. The appearances correspond with the fact that in the first case small patches of the kidneys are successively affected by local disturbances in the circulation in the kidney, in the second all the cells are at once subjected to the same destructive agent. All this suggests that arteriosclerosis is under such circumstances the primary cause of the nephritis, and not a result of the same. Whether nephritis may in its turn lead to a retention of toxic substances, these to an arteriosclerosis, and so to the establishment of a vicious circle is another question. While satisfactory experiments and clinical observations proving that nephritis is followed by an arteriosclerosis can hardly be said to exist, an enormous number show clearly enough that nephritis does follow arteriosclerosis. From all of which it is clear that the treatment of chronic interstitial nephritis (secondary to arteriosclerosis) calls not so much for a treatment of nephritis as for a treatment of arteriosclerosis, — and the more liberal rules laid down for the guidance of the patient with chronic interstitial nephritis than for him who suffers from any of the parenchymatous forms constitutes the tacit acceptance of this belief on the part of the therapist.[1]

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[1] The morphological changes that characterize chronic interstitial nephritis are in no sense specific. They represent the consequences of a progressive destruction of piece after piece of kidney parenchyma and replacement of this by scar tissue. Entirely similar pictures are obtainable in any gland in which the blood supply is cut down directly, or indirectly through ligation of the secretory duct, as *Dudley Tait* has shown.

3. Just as the arteriosclerosis associated with kidney disease is not to be discussed as the consequence, but rather as the cause of the kidney disease, so the *hypertrophy of the heart* observed in such cases is more the consequence of the arterial disease than of the kidney disease. This is clearly enough evidenced by the fact that the (physiologically) worst types of nephritis are those least liable to be

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[1] In spite of years of experimental work, the numerous observers who have tried to reproduce experimentally the picture of chronic interstitial nephritis in animals can scarcely be said to have been successful. Their failure resides in their methods, and it may safely be predicted that their present methods never can be successful. As must appear from the remarks made here, the picture of chronic interstitial nephritis will be produced only if a method is devised (analogous to the arteriosclerosis observed in the vessels of the kidney parenchyma) which will little by little destroy one fragment of kidney after the other. Injections of lead, arsenic, chromium, etc., do not attack the kidney in any such localized ways — they attack, generally speaking, all portions of the kidney equally and at once.

associated with any hypertrophy of the heart. That, on the other hand, enormous hypertrophies of the heart may be associated with no kidney symptoms whatsoever is familiar to everyone.

In discussing this subject of heart hypertrophy and chronic interstitial nephritis we seem, as clinicians, all too often to lose sight of the fact that the hypertrophy of the heart results in this case, as in any case, from the increased demands for work made upon the heart. In the hypertrophy associated with arteriosclerosis these increased demands result from at least two changes in the circulation: the reduction in the calibre of the blood vessels, and the loss of the elasticity of the blood-vessel walls.

It should be clearly borne in mind that the mere roughening of the blood-vessel walls has nothing to do with increasing the work of the heart. The friction encountered in driving the blood through the vessels is *not* that of blood against blood vessel wall. Since the blood " wets " the blood vessel walls the friction is that of one layer of liquid over another.

With a given kind of blood, the blood vessels determine how much energy is required to force the blood through them, only so far as their length (constant in body), diameter, and elasticity are concerned. So far as the effect of changes in diameter is concerned (and in arteriosclerosis the diameter of the blood vessels is diminished), it must be borne in mind that the force required to drive a given volume of liquid through a tube increases about as the cube when the cross section is diminished one-half. The loss of elasticity becomes a factor because, under physiological conditions, in the time of a single contraction of the ventricle an amount of blood, the equivalent of that ejected from the heart, is not at once pushed along the entire arterial and capillary bed out into the veins. Under normal circumstances it is simply thrown into the elastic arterial system which dilates somewhat, and then, during the period that follows the systole of the heart, the elastic forces resident in the arteries slowly recoil and squeeze the blood on out into the veins. When this elasticity is markedly diminished, the heart must in that proportion force its quota of blood during the time of each systole at once through the whole arterial and capillary system, and this demands an enormously greater outlay of energy.

A third factor for the hypertrophy of the heart might reside in the blood itself. A liquid moves through a tube with greater and greater difficulty the more viscid it is. Anything that would increase the viscosity of the blood would therefore increase the amount of work demanded of the heart to push the blood ahead. The viscosity of such colloidal solutions as the blood is enormously increased by slight traces of acid (*P. von Schroeder*,[1] *W. B. Hardy*,[2] and especially *Wolfgang Pauli* and *Hans Handovsky*[3]) and so this factor which comes into play not only in nephritis but in hard work of any kind (laborers, athletes) needs to be considered. While certain clinical studies of the viscosity of the blood have not as yet brought any proof to show that this undergoes any material change in nephritis, that such changes might well be expected is indicated by certain experiments of *R. Burton-Opitz*,[4] who found venous blood to have a higher viscosity than arterial, due to the CO_2 in it, and the blood of dogs after the feeding of proteins (acid production) to have a higher viscosity than before such feeding.

4. From what has been said it is clear that we cannot

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[1] *P. von Schroeder:* Zeitschr. f. physik. Chem., **46**, 106 (1903).

[2] *W. B. Hardy:* Journal of Physiology, **33**, 251 (1905); Proceedings of the Royal Society, **79**, 413 (1907).

[3] *Wo. Pauli* and *H. Handovsky:* Biochem. Zeitschr., **18**, 340 (1909).

[4] *R. Burton-Opitz:* Pflüger's Archiv, **119**, 359 (1907).

regard the heart hypertrophy as something primary, but as something secondary — as an example of the wide range of adaptation to changed conditions of which the cells and organs of our body are capable. The high blood pressure, far from being in itself an evil thing, is decidedly good — *only through the increased pressure are the various tissues of the body guaranteed a blood supply sufficient to satisfy their physiological demands.* This holds for the kidney as for any other organ in the body. Only the increased blood pressure renders it possible that the normal parts remaining in an arteriosclerotic kidney maintain what I have called the normal secretion of water from such a kidney. While conditions may exist or arise in the body which make the high blood pressure in itself dangerous (weakening of blood vessel walls and rupture), *a high blood pressure must with this exception not be regarded as something evil, but as an attempt on the part of the body to keep our various organs working at their physiological optimum.* Measures that *merely* reduce blood pressure can therefore hardly be looked upon with favor. *We must treat the underlying cause of the increased blood pressure, not the blood pressure itself.* To apply this to the kidney, with which we happen to be dealing here, I can recall several cases of chronic interstitial nephritis with high blood pressure and cardiac hypertrophy in which a too enthusiastic desire to reduce the blood pressure led to the use of the nitrites, and with serious consequences. While the blood pressure fell, the urinary output also decreased, the albumin rose, and casts became numerous. In other words, the general fall in blood pressure made for a decreased circulation of blood through the kidney, and so for an aggravation of the kidney state. Only when we think that such a bad result will not follow the use of nitrites are we justified in using them. One case developed immediately after a single dose of amyl nitrite a complete anuria which some eight days later killed the patient.

5. It remains for us to discuss the question of why the patient with chronic interstitial nephritis must rise to urinate at night. Such is the case even when there exist no pathological conditions in the lower parts of the urinary tract that might be considered responsible. But on the basis of our analysis, which makes chronic interstitial nephritis more an *atrophy* of the kidney than a nephritis (except in the small patches which are little by little cut out from the kidney), the matter is easily understood.

As the studies of *Bradford* have shown, we can spare some two-thirds or even more of our total kidney substance without serious inconvenience. It is in about such a state that the man with chronic interstitial nephritis finds himself. What must be the conditions for urinary secretion in such an individual? The normal man with all his kidney substance intact will secrete the five hundred, or say a thousand, cubic centimeters of water consumed with a meal in the two or three hours that follow this meal. The patient with only a third the normal kidney substance must take, other things being equal, three times as long to secrete this same amount of water, in other words, six to nine hours. While the normal man will be largely rid of the water he has drunk with his supper when he urinates for the last time before going to bed, the man with the chronic interstitial nephritis will continue to secrete urine into his bladder for hours afterward, and as this organ fills he must rise during the night to empty it.

3. The Secretion of Water by the Nephritic Kidney.

In support of the thesis that an abnormal accumulation or production of acid in the kidney constitutes the basic cause of every nephritis, it would be sufficient in this section merely to show that such a condition always leads to a decrease in the secretion of water by the kidney. We shall, however, not stop with this but try to indicate in a little more detail where lies the point of attack for the acid that is responsible for such a change in secretion.

It is an easy matter to show that *the direct introduction of acid into the kidney, or any method capable of leading to an abnormal acid content in the kidney, is followed by a decrease in urinary secretion which may go to the point of absolute stoppage.* This is clearly evident in the accompanying drawings which have been constructed from the experiments detailed in various parts of this paper.

Figure 22 on page 142 has been introduced to show the *normal* secretion of urine in three rabbits, kept on a mixed diet, when these are brought into the laboratory and are *loosely* tied into an animal holder. When the animals are *snugly* tied into a holder, the urinary secretion is decreased in amount. This is clear from Fig. 23, in which are shown the curves for the urinary secretions obtained in the animals that were rendered albuminuric by this means (Experiments 22, 23, 24, and 25). If instead of such a general state of lack of oxygen in the body we interfere locally with the blood supply to the kidney, as through clamping of the renal blood vessels, the same great fall in urinary output is observed, as is evidenced in the lowermost curve of Fig. 28. But to show that it is really the acid developed in the body as a whole, or in the kidney specifically, that under these circumstances is responsible for such a fall in secretion, it is best to inject the acid directly. The effect of such a proceeding is shown in Fig. 24 based on Experiments 12, 13, and 14. It would be purposeless to multiply these experiments to further support the contention that an abnormal acid content in the kidney leads to a decrease in the secretion of water. As a matter of fact, this finds daily corroboration in the decreased urinary output observed in all those clinical cases, such as heart disease, respiratory disease, etc., which we know to be associated with an abnormal accumulation and production of acids in the body.

But how may we imagine the acid to be effective in this regard? A proper answer to this question demands a critical review of all the various theories that have been proposed from time to time to explain the mechanism of normal urinary secretion, and this would lead us too far afield.[1] We can, however, help toward a more circumscribed formulation of the whole problem.

Defined physicochemically, the problem of water secretion by the kidney is essentially the problem of how water contained in the blood is made to pass through a solid (hydrophylic) colloidal membrane, this being represented, in the case of the kidney, by the various cells and their intercellular substances that lie between the blood on the one hand and the urine on the other. Two possible sources for the forces necessary to get the water through this membrane are available. The membrane may be perfectly passive and the blood itself suffer changes which result in driving the water through the membrane; or the membrane itself may be concerned in the process, in that it first absorbs water from the blood to give it up again later into the uriniferous tubules; or, finally, both may act together.

Two theories of urinary secretion that have considered changes in the blood as primarily responsible for the giving section merely to show that such a condition always leads to a decrease in the secretion of water by the kidney. We shall, however, not stop with this but try to indicate in a little more detail where lies the point of attack for the acid that is responsible for such a change in secretion.

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[1] See *R. Heidenhain:* Hermann's Handbuch d. Physiologie, **5**, Leipzig, 1883; *E. Waymouth Reid:* Schaefer's Textbook of Physiology, **1**, 261, London and Edinburgh, 1898; *E. H. Starling: ibid* **1**, 285; Oppenheimer's Handbuch d. Biochemie, **3**, 206, Jena, 1909; *H. J. Hamburger:* Osmotischer Druck und Ionenlehre, **2**, 93, Wiesbaden, 1904; *E. Overton:* Nagel's Handbuch der Physiologie, **2**, 774, Braunschweig, 1907; *O. Cohnheim: ibid,* **2**, 607; *R. Höber:* Korányi-Richter, Physikalische Chemie und Medizin, **1**, 295, Leipzig, 1907; *Martin H. Fischer:* Œdema, 186, New York, 1910; Kolloidchemische Beihefte, **2**, 304 (1911).

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[1] *Gottlieb* and *Magnus:* Archiv. f. exp. Path. u. Pharm., **45**, 223 (1901).

[2] *H. Bechhold:* Kolloid Zeitschr. **3**, 3, 33 (1907).

Very evidently, therefore, if we note changes in urinary secretion with changes in blood pressure, the secretory changes are not to be attributed to the changes in blood pressure *per se*, but to some of the accompaniments of such changes in blood pressure. *Heidenhain* expressed this thought by saying that it was not the pressure which determined the secretion, but the amount of blood passing through the kidney. But this also does not adequately express the problem. It is not alone the amount of blood but the kind of blood. Only when blood rich in oxygen and low in carbon dioxide goes through the kidney do we have secretion. No amount of venous blood going through the organ will yield a drop of urine. Since the blood does not carry its great oxygen content for its own benefit, and since the arterial blood which enters the kidney leaves this organ as venous blood, it is clear that the cells here use it up, and since the kidney actively secreting water uses up more oxygen and yields more carbon dioxide[2] than a resting kidney, it follows that ***this secretion demands work on the part of the kidney structures—the secreting colloidal membrane.*** Further evidence that the kidney does such work is furnished by the higher temperature that prevails in the urine over that prevailing in the blood from which it is derived.

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[1] The recent experiments of *Alfred Schoep*, Kolloid Zeitschr., **8**, 80 (1911), can also not be called upon for help. That *Schoep* got a filtration of water through collodion membranes with only a few millimeters of mercury pressure constitutes an experimental fact that cannot immediately be used for biological purposes. Collodion is a lyophilic colloid in such solvents as ether, alcohol, etc. It is a lyophobic one in water and therefore does not represent a membrane at all of the nature of those existing in the living animal (which are lyophilic in water).

[2] See *Barcroft* and *T. G. Brodie:* Journal of Physiology, **32**, 18 (1904); **33**, 52 (1905).

A second theory of urinary secretion that regards changes in the composition of the blood as of primary importance in determining the secretion of water from the kidney is that proposed by *Isador Traube.*[1] According to this author, changes in the surface tension of the blood are responsible for a squeezing of fluid through the capillary structures composing the kidney (the cells and intercellular substances) that lie between the blood on the one hand and the urine on the other. The ingenious ideas of *Traube* have scarcely received the attention from physiologists and pathologists that they deserve. In connection with our problem I should only like to point out that should they ultimately prove adequate to account for the phenomena of secretion — a subject of doubt to my mind, chiefly because during secretion the secretory membrane does work and in proportion to the amount of secretion, while *Traube's* ideas do not demand this — the introduction of acid into the blood or into the kidney would be associated with such changes in the surface tension of the blood and in the capillarity of the kidney as to render the changes in secretion observed in nephritis readily intelligible.

The theories of urinary secretion which lay the main stress upon the kidney cells themselves, as the sources for the energy required to separate water from the blood, may be briefly considered under three heads — the "physiological" or "secretory" theory, the osmotic theory, and the colloidal theory.

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[1] *Isador Traube:* Pflüger's Archiv, **105**, 541 (1904); **123**, 419 (1908); **133**, 511 (1910); Biochem. Zeitschr., **10**, 371 (1908); **16**, 182 (1909).

The "physiological" or "secretory" theory of urinary secretion suffers from the defects of every such "physiological" theory — it explains nothing. The osmotic theory suffers through its inadequacy. In spite of all one's reluctance to give it up, when one considers its tempting simplicity and the wealth of biological fact that its discussion and experimental study have yielded, it seems now as though it would scarcely be able to maintain even a partial rôle in the phenomena of water absorption and secretion as observed in plant or animal cells.[1] If the osmotic theory of absorption and secretion has to be relinquished in working with individual cells, it will have to go all the more certainly in the special problem of absorption and secretion as presented to us in the kidney.

I have suggested that the explanation of urinary secretion be sought in the colloidal constitution of the kidney and in the physicochemical changes that this suffers under the various conditions which we know to influence the secretion of water from this organ.[2] The separation of water from the blood by the urinary membrane) that is, all the structures that lie between the blood on the one hand and the urine on the other) involves two processes — an absorption of water from the blood, and a subsequent giving off of this same water out into the uriniferous tubules. How is this accomplished?

As already pointed out, the urinary membrane is built up of a series of (hydrophilic) emulsion colloids. That half of the process of urinary secretion which consists of an absorption of water from the blood by the urinary membrane is entirely analogous to the absorption of water by fibrin, gelatine, or serum albumin, — technically put, it consists of a hydration of some or all of the (hydrophilic) emulsion colloids composing the kidney. The other half of the process of urinary secretion consists in a giving up of this absorbed water; it is analogous to the loss of water by fibrin, gelatine, or serum albumin, in other words, to the dehydration of a (hydrophilic) emulsion colloid. To accomplish the secretion of urine a cycle of changes must therefore occur in the kidney, which leads first to the absorption of water and then to its secretion. Let us ask of what such a cycle of changes might consist, and though in the case of the kidney we venture here upon treacherous ground, a few experimentally well-established facts point out a road rather clearly.

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[1] See *Wolfgang Pauli:* Sitzungsberich. d. Wiener Akad. Math-naturw. Klasse, **113**, 38 (1904); *Martin H. Fischer:* Physiology of Alimentation, 182–187, 267–269. New York, 1907; Œdema, 85. New York, 1910.

[2] *Martin H. Fischer:* Œdema, 180. New York, 1910.

In discussing the problem of *absorption*,[1] which apparently is to be regarded in every sense as the mirror image of secretion, I pointed out how the carbonic acid production in cells may be one — or under physiological conditions the chief — factor in determining the absorption of water from the peritoneal cavity or the intestinal tract. Experimental observations seem to indicate that the following happens: the cells of the peritoneum or of the intestinal tract produce carbonic acid. This increases the hydration capacity of the colloids constituting the peritoneum or intestinal tract for water, and so if any is present in either location it is absorbed. But the arterial blood entering the peritoneum or the mucous membrane of the intestine has a lower carbon dioxide tension than that found in the cells here, and so this diffuses over into the blood. As this enters the blood the capacity of the blood colloids for holding water is increased (as is evidenced microscopically by a swelling of the blood corpuscles in a venous blood, and physicochemically by an increase in the viscosity of the blood). Between the increased capacity of the blood to carry water, and the now diminished capacity of the cells of the peritoneum and intestinal tract to hold on to it, the water previously absorbed from the peritoneal cavity or the intestinal lumen is now dragged over into the blood. As long as the circulation is maintained water must therefore be absorbed from the peritoneum or the lumen of the intestine, and as steadily be lost on the opposite side of the absorbing membrane into the blood.

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[1] *Martin H. Fischer:* Kolloidchemische Beihefte, **2**, 304 (1911).

In the case of the kidney, a reverse series of changes brings about a secretion of water. To render secretion possible we must first of all supply the kidney with oxygen. In the process of water secretion by the kidney this oxygen is not only used up but carbon dioxide is produced, and the loss of one and the production of the other run the higher the greater the amount of water secreted by the kidney.[1] In the carbon dioxide production in the cells of the urinary membrane we have, therefore, the establishment of conditions which increase the capacity of the colloids here for absorbing water. In the loss of this same carbon dioxide to the blood we have subsequently the cause for the loss of the previously absorbed water out into the space of *Bowman's* capsule or the uriniferous tubules. The only part of water secretion by the kidney that this simple interpretation does not explain is why the water is lost toward the lumen, and not back into the blood with the carbon dioxide. But for this a simple explanation (based on certain anatomical relationships existing in the kidney and on differences in rates of diffusion) can also be given, as I hope to show at another time in discussing some colloidal models of secretion.

As I have previously pointed out,[2] the kidney is not alone involved in this matter of urinary secretion, but the blood as well, and, somewhat more remotely, all the tissues of the body. We have already touched upon the fact that only arterial blood will yield a secretion, and that no amount of venous blood will do so. But aside from this important fact it must always be borne in mind that the mere coursing of blood through the kidney does not represent the existence of an inexhaustible fountain of water out of which urine can be manufactured as is so frequently done by physiological and clinical workers. The water found in the blood is ordinarily to be regarded as bound to the colloids of the blood. Only as these suffer a change which makes them incapable of holding as much water as they once did, or the colloids of the urinary membrane develop an avidity for water that overtops that of the blood colloids for this same water, does water from the blood become available for absorption (preparatory for secretion) by the kidney. The body tissues generally play a rôle in the whole problem as they give up or take water away from the blood. Other things being equal, it is evident that the kidney will secrete water the more easily, the less firmly it is bound to the colloids of the blood.

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[1] *Barcroft* and *T. G. Brodie:* Journal of Physiology, **32**, 18 (1904); **33**, 52 (1905).

[2] *Martin H. Fischer:* Œdema, 184. New York, 1910.

These remarks have all been necessary in order to show why it is that the abnormal production or accumulation of acid in the kidney, as occurs in nephritis, must be followed by a decrease in the secretion of water (urine) from the kidney. The acid must interfere, first of all, with the chemical (enzymatic) changes in the kidney cells themselves, which are responsible for the normal oxidation processes that occur here (such as the production of carbon dioxide). While such an increase in the amount of acid held in the kidney as occurs in nephritis, does not interfere with the absorption of water from the blood, favors it, rather (as evidenced by the swelling of the kidney), it interferes decidedly with the subsequent loss of the absorbed water which constitutes the palpable external evidence of secretion. The loss of the acid to the blood must be rendered the more difficult the higher the amount of acid already present here, — wherefore the question of the amount of acid contained in the body as a whole becomes an important factor in the problem of nephritis. As a final word let us point out the fact that the nephritic kidney in swelling (as it possesses a firm capsule) compresses its vascular supply. In consequence of this it not only decreases, through the decrease in the absolute amount of blood going through the kidney, its opportunities for losing such acid as it has already accumulated, but places its component cells in a position where an abnormal acid production is immensely favored (lack of oxygen). All these facts must be borne in mind, and point the way to be followed when we come to discuss the matter of treatment.

4. The Changes in the Secretion of Dissolved Substances by the Nephritic Kidney.

As already noted, the nephritic kidney shows deviations from the normal secretion of dissolved substances by it in two directions. There is, first of all, a decrease (other conditions remaining the same) in the absolute amounts of the various substances secreted, and second, in the relative proportion that these bear to each other when compared with the secretion of these same substances as observed in health. The nephritic kidney secretes some substances as well as does the healthy kidney, others decidedly less well. It is our problem to say how such a condition as an acid production in the kidney brings such a state of affairs to pass. In order to do this we must recall some of the facts of normal secretion by the kidney.

As is familiar to everyone, a secretion of some substances proportionately more easily than others, in other words, a "selective" secretion by the kidney, such as we have just outlined, is not characteristic of the diseased kidney, but of the healthy kidney as well. This is really the rock on which most of the mechanical, or to use a broader and better term, nonvitalistic or physicochemical conceptions of urinary secretion have foundered, — and these founderings have given momentary comfort to those who believe that kidney secretion, as many another physiological phenomenon, is "vital" in character. But such a pessimism would seem to be premature, for we are already familiar in physical chemistry with not a few systems in which differences in the concentration of any substance are easily maintained over indefinitely long periods of time, and, of course, without the assistance of those "peculiar" forces believed by some to inhabit the living cell. Reference is here made to *the differences in the distribution (distribution coefficient) of any substance between two phases.*

Through the work of *Hans Meyer* and *E. Overton* the differences in the solubility of such substances as alcohol, ether, chloroform, morphine, cocaine, etc., in water and in fats and fatlike bodies (lipoids) — their distribution coefficients between two solvents — have been shown to explain very satisfactorily why these substances not only diffuse with greater speed into and through cells, especially rich in the fatlike bodies (the fat cells and the cells of the central nervous system), than into and through such as contain these in smaller amounts (yellow elastic tissue, white fibrous tissue), but why in the end they are found in larger absolute amounts in some tissues than in others.

A second property of protoplasm which permits one cell or tissue to take up more of any given substance, and this more speedily than is the case with another cell, is the character of the colloids contained in the cells and the state in which these find themselves. This is one of the reasons why certain stains when injected intravenously are not taken up with the same speed, or to the same extent, by all the tissues of the body.

A third property of protoplasm, which makes for inequalities in the distribution of a substance, resides in the chemical differences existing between different kinds of protoplasm. Certain of the "vital" and "specific" protoplasmic stains are examples of this class. In these a chemical combination results between the dye and the chemical compounds found in some cells.

What use can we make of these facts in the explanation of the alterations observed in the secretion of dissolved substances by the nephritic kidney? In proposing a colloidal theory of urinary secretion,[1] I have tried to show how the "selective" character of secretion may be explained in the following way:

All secretion of dissolved material by the kidney is dependent, first of all, upon a secretion of water by the kidney. After the water is secreted I hold that all the constituents which characterize it as urine come to be added to it, in its course through the uriniferous tubules, by a process of leaching out of the dissolved substances present in the kidney cells. But in this process of leaching out not all the constituents present in the protoplasm leave the cells in which they are originally present with the same ease. Depending upon the character of the dissolved substance, and the state of the protoplasm as to lipoid content, colloidal state, and chemical composition, the water present in the uriniferous tubule may come to take up the dissolved substance to an extent which allows it ultimately to be found here in a lower concentration than in the kidney cells, in the same concentration, or in a greater one. It is all a matter of equilibrium. But the equilibrium points with different substances are different, and so the relative amounts of these different substances that appear in the urine are also different. In other words, the (normal) leaching out is " selective," or, to put it biologically, the " secretion " of the dissolved substances is selective.

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[1] *Martin H. Fischer:* Œdema, 180. New York, 1910.

But this leaching out of dissolved substances from the kidney is only one-half of the process of urinary secretion. The other half is the process of the absorption of dissolved substances from the blood by the kidney cells preparatory to their secretion into the lumen of the uriniferous tubules. This is also a selective process, and here the same laws of lipoid solubility, colloidal adsorption, and chemical combination, which have already been discussed in the leaching out process, again come into play.

All these various processes of absorption and secretion of dissolved substances by the kidney cells are most markedly influenced by the reaction existing in them, and it is for this reason that the observed variations from the normal in the secretion of dissolved substances by the nephritic kidney occur.

It is easily appreciated why there must be a decrease in the *absolute amount* of dissolved substance secreted by the nephritic kidney. If the secretion of water through the kidney is diminished, then clearly not as much dissolved substance can be leached out of the kidney parenchyma as when more is secreted. Into this, however, enters the element of *time*. When much water is being secreted by a kidney its discharge into the pelvis of the kidney is also hastened. The time that a given portion of the urine (secreted as water initially) is in contact with the kidney cells is thereby diminished, and so not all that this water is *capable* of absorbing is taken up. When the water is secreted more slowly, the ultimate equilibrium point for the distribution of dissolved substances between the kidney

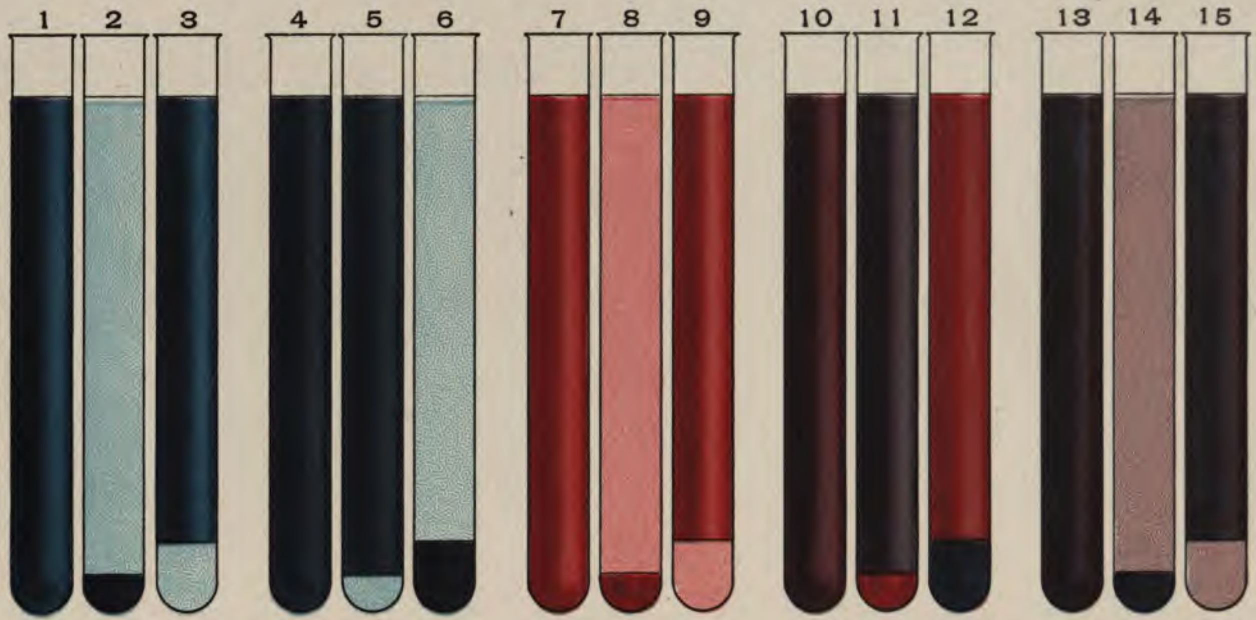

Figure 21

and the urine is more nearly approximated. We find daily expression of this fact in the clinical observation that after the consumption of much water the concentration of the urine falls, while with a diminished intake of water, or when the kidney cannot secrete it (as in nephritis), the concentration of the urine becomes progressively higher. Yet, other things being equal, the absolute amount of any dissolved substance secreted by the kidney must be the greater, the larger the absolute amount of water secreted by the kidney in any unit of time.

To illustrate how the increased acid content in the kidney in nephritis leads to variations in the secretion of the dissolved substances, I would like to introduce a few simple test-tube experiments and experiments on rabbits, which concern themselves particularly with that part of the selective secretion which deals with the colloidal state of the kidney cells. This constitutes by far the most important part of the whole problem of selective absorption and secretion, for the state of a colloid in the body is more easily affected by external conditions than is the solvent property of a lipoid, or the chemical character of any part of living protoplasm. As the various dyes betray themselves not only qualitatively, but, in a sense, also quantitatively, to the naked eye, illustrations of the " absorption " and the " secretion " of these, under conditions that interest us in our discussion of nephritis, seemed to me best suited to our needs. I chose, moreover, dyes that have been used physiologically in the study of the kidney. The results of a few experiments on the staining of fibrin, which are familiar to any worker who has at all touched upon the problem of dyeing, and which might be multiplied indefinitely by using other dyes and different colloids, are shown in Fig. 21.

Tube 1 contains an aqueous solution of toluidin blue.

If into another tube (2), containing the dye in the same concentration, some powdered fibrin is dropped, this soon absorbs most of the dye and stains intensely blue. The supernatant liquid retains only a faint tinge of the blue but this remains indefinitely. If the supernatant solution is carefully pipetted off, and distilled water is placed over the dyed fibrin, the water now slowly turns blue. In this way, through successive washings, we can again get considerable of the blue out of the fibrin. In other words, the fibrin absorbs the dye until an equilibrium is reached between the concentration of the dye in the fibrin and the concentration of the dye dissolved in the supernatant liquid. If now we disturb this equilibrium by removing the blue solution above the fibrin and substituting water for it, some of the dye comes out of the fibrin until equilibrium is once more established.

If we will now write kidney colloids for fibrin we have what happens in this organ when it secretes any dye. The absorption of the dye by the kidney cells from the blood is analogous to the first series of changes that we describe, the leaching out of the dye by the urine to the second series. We can also see at once why the quantity of urine secreted and the time that this remains in contact with the kidney cells are of such importance. This corresponds with the renewal of the distilled water above the dyed fibrin and the time this is allowed to remain there before being pipetted off.

What happens if we introduce into this whole system a trace of acid? The result is shown in tube 3. The fibrin swells somewhat, but the toluidin blue is now scarcely taken up. The supernatant liquid remains practically as blue as the control tube 1. What would this mean when applied to the kidney affected with nephritis, for which we have maintained that an abnormal acid content is responsible? That the kidney would swell as does the fibrin, with this we are already familiar. But such a kidney would now not absorb the toluidin blue preparatory for secretion as does the healthy kidney. On the other hand, we must not hastily conclude herefrom that under such circumstances the kidney would necessarily also secrete this dye badly. Once any dye was in the kidney colloids this would rapidly diffuse into the urine, not only because the kidney colloids are not holding on to the dye particularly firmly, but because the acid liable to be in such urine as is secreted from the nephritic kidney would further favor the passage of the dye into it.

In tubes 4, 5, and 6 are shown a parallel series of experiments carried out with sodium indigosulphonate. It is clear that with this dye conditions are exactly the reverse of those obtaining in the case of toluidin blue. The very circumstances which favored absorption before, hinder it here, and those which hindered it before now favor it. In tubes 7, 8, and 9 are shown the results obtainable with neutral red, which, it will be observed, behaves like toluidin blue.

But the kidney is not thus offered one substance at a time to secrete into the urine. The blood that passes through this organ brings it many at once. What must be the behavior of the tissue colloids under such circumstances? As tubes 10, 11, and 12, and tubes 13, 14, and 15 clearly show, a colloid under such circumstances behaves toward each of the substances offered it as though the others were not present. In tube 10 is shown the effect of mixing sodium indigosulphonate and neutral red. If some fibrin is introduced into this mixture it absorbs the red (chiefly) and leaves behind (almost) all the blue. This would correspond with the kidney function in health. If now an abnormal amount of acid were present in the kidney (nephritis) just the reverse would result — the red would now be left behind in the blood, while the blue would be absorbed.

In tubes 13, 14, and 15 are shown the results on the staining of fibrin when toluidin blue and neutral red are mixed. The resulting color is shown in tube 13. In the presence of fibrin both of the dyes are absorbed as shown in tube 14, but if a little acid is present, or is subsequently added, the fibrin fails to stain. Figure 21 was painted from the results obtained in the following Experiment 21, after the tubes had stood some eighteen hours. Marked differences in the degree of staining are readily visible, however, after ten minutes.

EXPERIMENT 21.

1. 15 c.c. .01 per cent toluidin blue plus 15 c.c. water.
2. 15 c.c. .01 per cent toluidin blue plus 15 c.c. water plus 0.4 gram fibrin.
3. 15 c.c. .01 per cent toluidin blue plus 15 c.c. $\frac{1}{20}$ normal acetic acid plus 0.4 gram fibrin.
4. 15 c.c. .02 per cent sodium indigosulphonate plus 15 c.c. water.
5. 15 c.c. .02 per cent sodium indigosulphonate plus 15 c.c. water plus 0.4 gram fibrin.
6. 15 c.c. .02 per cent sodium indigosulphonate plus 15 c.c. $\frac{1}{20}$ normal acetic acid plus 0.4 gram fibrin.
7. 15 c.c. .02 per cent neutral red plus 15 c.c. water.
8. 15 c.c. .02 per cent neutral red plus 15 c.c. water plus 0.4 gram fibrin.
9. 15 c.c. .02 per cent neutral red plus 15 c.c. $\frac{1}{20}$ normal acetic acid plus 0.4 gram fibrin.
10. 15 c.c. .02 per cent sodium indigosulphonate plus 15 c.c. .02 per cent neutral red.
11. 15 c.c. .02 per cent sodium indigosulphonate plus 15 c.c. .02 per cent neutral red plus 0.4 gram fibrin.
12. 7½ c.c. .04 per cent sodium indigosulphonate plus 7½ c.c. .04 per cent neutral red plus 15 c.c. $\frac{1}{20}$ normal acetic acid plus 0.4 gram fibrin.
13. 15 c.c. .01 per cent toluidin blue plus 15 c.c. .02 per cent neutral red.

14. 15 c.c. .01 per cent toluidin blue plus 15 c.c. .02 per cent neutral red plus 0.4 gram fibrin.

15. 7½ c.c. .02 per cent toluidin blue plus 7½ c.c. .04 per cent neutral red plus 15 c.c. $\frac{1}{20}$ normal acetic acid plus 0.4 gram fibrin.

The details of this experiment have already been discussed in the text.

It follows from all this that the presence of a little acid in such a colloidal material as that which we know to compose the kidney must be followed by profound changes in the character of the secretion of dissolved substances by this organ as compared with the normal secretion of these same substances. But depending upon the way in which the acid displaces the equilibrium point it is clear that, with otherwise constant conditions, the secretion of any substance may not only be decreased or simply remain unaffected, but it may actually be increased. With illustrations of the first two of these possibilities we are familiar from the analyses of the urine in nephritis. Examples of the third have not yet been sought for.

Before closing this chapter it is well to refer to a few animal experiments which show that what has been said above regarding the staining of fibrin actually holds in the case of the living animal. As pointed out in our discussion of the experiments of *Heidenhain*, *Dreser*, and *Nussbaum*, these authors found the kidneys of their experimental animals stained most deeply, and most generally with sodium indigosulphonate or acid fuchsin (which stains fibrin just as does sodium indigosulphonate) when conditions favoring the accumulation of acid in the kidney were most clearly at hand. This corresponds with the improved tendency of fibrin to stain with these dyes when an acid is present. When in a rabbit under morphine anæsthesia the artery to one kidney is clamped for an hour or two, and then *sodium indigosulphonate or acid fuchsin* is injected intravenously, while the clamp is removed from the artery, it is found that *the clamped kidney not only stains sooner than the unclamped one, but more intensely.* When now frozen sections are made of the two kidneys the dye in the healthy kidney is found only in the lumina of the uriniferous tubules, while in the ligated kidney it is found in the cells themselves. And yet a kidney so clamped for an hour or two will not yield any urine for hours afterwards, if ever again. *The staining of the kidney, as already once noted above, is therefore not an index of secretion, but in this case rather of its lack.*

The reverse of this experiment can be done with *neutral red.* Here the normal kidney stains well and rapidly, while *the clamped one remains without color,* owing to the acid developed in it in the absence of a circulation. Clearly, therefore, mere staining of a cell can by itself tell us little regarding the *secretion* of such a stain by that cell.

After what has been said it must be self-evident that too many factors enter into the picture of the secretion of any dissolved substances by the kidney — too many factors at which we can to-day but guess in a clinical case — to make any conclusions regarding the functional activity of the kidney, as derived from a study of the elimination of some one compound swallowed by the patient and sought for in his urine, of any material value. Even though we ignore all other elements of error, the state of the blood, the state of the kidney colloids, and the state of the urine all influence the rapidity and perfection of the elimination of the substance in so marked and (for us) uncontrollable a way, that trustworthy conclusions are impossible, and when we take the liberty, as is so often done, of applying what we may have learned from the elimination of one substance without modification to some other or all other constituents found in the urine, then we are on dangerous ground indeed. Until we have learned far more regarding the laws that govern the secretion of dissolved substances by the kidney than we know to-day, *we had best accept as the most reliable test for the functional activity of this organ its ability to eliminate water.*

IV. ON THE TREATMENT OF NEPHRITIS.

For the treatment of nephritis everything has been suggested; a discussion of the subject can scarcely, therefore, hope to bring the mention of anything new that might be tried. It can hope to be of interest or importance only as on the basis of the views entertained by an author regarding the nature and the cause of nephritis he will assign to certain practices grades of importance different from those assigned to these same practices by another — a difference of opinion that may perhaps be carried to the point where the one will find virtue in procedures that another regards only as evil, and vice versa. It is not our purpose in these pages to discuss the whole question of the therapeutics of nephritis, but on the basis of what has been written we may advantageously take up a few points in this field. In so doing we will discover further support for the conception of nephritis that has been advanced in the preceding pages.

1. Some General Considerations.

Were we to formulate a general rule for the prophylaxis and for the treatment of nephritis we would evidently have to say that this lies in *an avoidance, as far as possible, of every condition that favors the abnormal production or accumulation of acid in the kidney.* What such a rule would mean in the language of every day is easily seen.

We have long paid attention to the *diet* in this matter of nephritis. Clearly, the direct consumption of *acid* by the nephritic individual is contraindicated. The mineral acids which would be worst in this regard do not enter into our foods to any appreciable extent, though in the forms of fruits, sour wines, etc., not inconsiderable amounts of organic acids are swallowed. Most of these undergo oxidation in the body rather easily and are converted into carbonic acid which, under ordinary circumstances, is readily excreted. The organic acids are therefore less poisonous than might at first appear, but from this is not to be concluded that they are of no importance at all in the consideration of this subject of nephritis. Not only are certain "weak" organic acids (notably tartaric, acetic, and lactic) quite as active *physiologically* as the "stronger" acids, but consumed in excessive amounts they are not without effect, as witness the œdema observed in children that are fed buttermilk,[1] the urticarias following the consumption of excessive amounts of grapes,[2] etc.

In the metabolism of *proteins* not inconsiderable amounts of acid are produced.[3] Herein is to be sought at least part of the explanation of why a restriction of the proteins in nephritis is of use. The fats also yield acids when digested and so may the carbohydrates under certain circumstances. But before one proceeds to a too drastic revision of the dietary, a process in which we are particularly liable to eliminate the proteins too vigorously, the absolute amounts of acid formed by the various constituents of the food should be considered. When this is done it will be found that the evil consequences expressed in terms of a *direct* acid yield from the proteins of our food, for example, are small compared with those that may be calculated from a bottle of dry wine. Consideration of the acid content of alcoholic beverages helps us moreover to understand why some of these exercise a worse effect in nephritis than others. We have long recognized that the alcohol content is not alone responsible for the effects of alcoholic beverages in kidney disease, for while it is true that in large doses alcohol allies itself with the general anæsthetics, small doses do not interfere with the oxidative reactions in the living cells, but rather favor these (and so kidney function). But whatever is fed, it is clear that all the acid effects of the food need not appear if we will take the precaution of seeing that the diet contains sufficient alkali to neutralize the acid.

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[1] *Ernst Schloss:* Deut. med. Wochenschr., No. 22. (1910). *Schloss* does not, however, consider this an œdema due to feeding acid, but as "idiopathic." He found it to disappear on administering calcium salts.

[2] Personal observation. The urticaria disappears as soon as calcium salts are given, or fails to appear entirely if such are consumed with the grapes.

[3] *G. von Bunge:* Zeitschr. f. Biol., **10,** 111 (1874); *N. Lunin:* Zeitschr. f. physiol. Chem., **5,** 31 (1881); *Emil Abderhalden:* Biochem. Zentralbl., **2,** 257 (1904). See also the important studies on the balance of acid-forming and base-forming elements in food by *H. C. Sherman* and *A. O. Gettler:* Proc. Soc. Exp. Biol. and Med. **8.** 119 (1911).

The rôle of *hard work* as a factor in inducing nephritis, or aggravating an already existing one has been too long recognized to demand any special comment. Muscular work and, less obviously, mental work lead to an enormous acid production in the body. Sufficiently hard work makes any man show all the symptoms and signs of a nephritis. Under normal circumstances the acids produced in muscular or mental endeavor are quickly oxidized and leave the body in the form of carbon dioxide. But for this a plentiful oxygen supply is demanded, and when this is not furnished, as in close rooms and factories, then such conditions become factors in our problem of nephritis. Let now an anæmia[1] be added and we have built out of a few circumstances, each simple enough in itself, a vicious circle that has in it all the possibilities of speedy death. How a heart lesion, or an anæsthetic, or a drinking bout, or exposure to cold may push the acid content of the kidney up to the point where it can care for it no longer is self apparent.

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[1] A satisfactory explanation of why an anæmia is so often associated with nephritis has not yet been given. The anæmia is a prominent sign only in the parenchymatous types of nephritis — those that have an œdema. This, it seems to me, is not an accidental combination. May we not regard the acid which yields the kidney changes and which is to be held responsible for the œdema of the tissues generally also responsible for the anæmia, in that it behaves like a "hæmolytic" agent? See my remarks on the nature of hæmolysis [Kolloid Zeitschr. **5**, 146 (1909) or Œdema, 166 (New York, 1910)].

Just as we have seen how certain circumstances favor the development of a nephritis so also can we see how others counteract this. Most notable here are the long observed beneficent effects that follow the use of *alkalies* and the substitution of a more strictly *vegetarian diet* for our ordinary mixed diet. The alkaline mineral waters are of course capable of pushing the equilibrium existing in the kidney between the hydrogen ions and the hydroxyl ions toward the hydroxyl side, and so of counteracting that rise in acidity here which we consider lies at the bottom of nephritis.

A diet rich in vegetables helps our nephritic in part in the same way as though he consumed alkalies directly. The bases present in vegetables are combined with weak organic acids; in other words, the vegetables contain salts which when dissolved in water are alkaline in reaction. In the body these organic acids are largely oxidized to carbonates and so the tendency of the body tissues to become alkaline in reaction is still further developed. How successfully a diet rich in fruits and vegetables counteracts even the normal tendency of the body to become acid is a matter of common knowledge to any physician who has watched the urine of any patient turn from its normal acidity to an alkalinity, when ordered from an ordinary mixed diet upon one richer in the vegetables and fruits.

But I would like to insist that this neutralization capacity of the vegetable diet for acids is not the only factor to be considered in accounting for its beneficent effect in nephritis. We learned earlier in this paper that the solubility of protein in any acid is markedly reduced by salts. Not only are the vegetables rich in salts but they are rich in the very ones which act most powerfully in reducing the solubility of the protein. So we may find in this fact, along with what has already been said regarding the capacity of the vegetable diet to neutralize acids, a satisfactory scientific foundation for the reduction of the albuminuria in *Bright's* disease, when a diet rich in vegetables follows one in which these were not so abundant. Such salts also serve to reduce the size (swelling) of the kidney, and as we have seen, they practically prevent those precipitation effects in the kidney cells (granule formation) that are characteristic of the early changes of nephritis from a morphological point of view. Speaking generally, a diet high in vegetables also means that the individual is consuming more water. The effect of this will next be discussed, and later we shall return once more to the question of salts in the diet.

2. Water Consumption in Nephritis.

The question of water consumption resolves itself into two parts, on the one hand, into the use of water in cases where a nephritis is likely to arise, on the other, to its use in an established case. From all that has been said it must be clear that *the intake of water should never be restricted.* To this rule there exists to my mind only one possible exception, and that is the advisability of stopping water TEMPORARILY — say for an hour or two for reasons that will appear later — in cases of complete suppression of the urine. *Neither does this statement mean that pure water is necessarily the best form in which to take this,* but with this matter we will deal immediately. The reasons why water should be given without restriction are obvious. No matter with what condition we are dealing that we may consider liable to lead to a nephritis, what produces that pathological state in the end is an intoxication. This is strikingly true of course in the infectious diseases or in an eclampsia case. Here the whole organism is suffering from the effects of a poison. The effect of that poison depends not alone upon the length of time that it acts upon the organism as a whole or any individual part of it, but upon the *concentration* of the poison present at any one time. If now our interest centers upon a toxic effect that such a poison may have upon the kidney, and we are anxious to protect this organ, it is clear that the concentration of the poison must be kept as low as possible in this organ. To do this we have only two possibilities open to us and when we cannot control the factor of poison production, we can hope to cut down the effect of the poison only by keeping what is produced as dilute as possible, which means the giving of water. In this connection the practical point should be remembered that in ordinary practice an ever so patient administration of water through the day is likely to be neglected in the night. As toxine production does not cease with nightfall, it is clear that water administration also should not, otherwise we are likely to lose in a few hours at night what we cannot subsequently regain in days, if at all.

At this point we are likely to be met by the argument that while such a water therapy is accepted as advisable in the toxic nephritides, those associated with heart lesions, etc., are not to be similarly treated. Let us first point out the fact that these too are toxic nephritides — the patient with a broken heart compensation, or a compressed lung due to a carcinomatous pleurisy, and albumin in his urine shows this (according to our views), because the acid content in his kidneys is abnormally high. The more the concentration of this can be reduced the less will be its effect on the kidneys. Thus far, therefore, he needs water quite as much as the nephritic who is such in consequence of an infectious disease.

But it will be argued that the giving of water increases the work of the heart in these cases, and so is bad. Let us consider this problem dispassionately. The belief that the giving of water increases the work of the heart is based upon the notions of urinary secretion, which imagine that water is pushed through the kidney cells by gross mechanical means. And so it is reasoned that the more water that is given, the more push is required, that is to say, the more blood pressure, and so the more work from the heart. Actually such a belief lacks every experimental support. If one fact regarding urinary secretion stands out as well established, it is that the forces active in producing the urinary secretion lie within the kidney itself. The only thing therefore that we might call upon as responsible for increasing the work of the heart would be some *product* of the work of the kidney in separating urine from the blood. We have a right to consider here the effect on the heart of the extra carbon dioxide[1] produced whenever the kidney functions. But the effect of this cannot be greater than that of an equal amount produced normally, or in a given case of kidney disease than an equal amount produced in some other organ. And when compared with the total amount of carbon dioxide produced from all other sources, the amount of carbon dioxide produced in the kidney because of the consumption of a few extra liters of water is small indeed.

Even were we to admit that the effect of such an increased carbon dioxide production by the kidney did markedly increase the work of the heart — a view for which we have not a single unequivocal clinical observation — it would still have to be proved that such an effect is worse than that resulting from an accumulation of acid in the kidney (and in the body generally) because of an insufficient elimination of water through the kidney. As a matter of fact, we know this reasoning to be sound from the fact that the parenchymatous types of nephritis, in which water elimination is most decidedly insufficient, and in which it would be expected in consequence that the heart would be working hardest in order to rid the body of any consumed water, are the very types in which heart complications (hypertrophy) are most conspicuously absent.

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[1] *Barcroft* and *T. G. Brodie:* Journal of Physiology, **32**, 18 (1904); **33**, 52 (1905).

Let us now ask if in the chronic interstitial types of nephritis this rule of no water restriction also holds good. We have sufficiently dilated upon the fact that chronic interstitial nephritis without urinary findings is not physiologically a nephritis. When albumin, casts, and œdema appear, that which we have just said for parenchymatous nephritis holds for it. But what is to be our position when the urinary findings are absent?

As we have already pointed out, the work done by the heart in pumping blood through the blood vessels depends upon the length, diameter, and elasticity of the blood vessels, and upon the viscosity of the blood. The giving of water certainly does not affect the first three factors. So far as viscosity is concerned, it can only decrease this and so ***diminish*** the work of the heart, as diluting a syrup with water makes it easier to draw it through a straw. If we are willing to admit that in consequence of the general circulatory disturbances in our patient with chronic interstitial nephritis the increased work thrown upon his heart is in part due to an increase in the viscosity of his blood occasioned by the presence of abnormal amounts of acid in it, then the giving of water must again be of help, for this aids in decreasing the concentration of the acid.

The only objections that may be raised against a too vigorous administration of water, it seems to me, are two. The first is associated with the fact that in the parenchymatous types of kidney disease the kidney swells; the second with the effect of the water in washing out salts. We have already said why the swelling occurs in nephritis — the abnormal acid content of the kidney cells increases the capacity of their colloids for water, and consequently if this is offered them they swell. And so it might be reasoned that to give water in the acuter forms of nephritis would be to aid this swelling. Such swelling of the cells, so far as the *cells themselves* are concerned, can hardly be considered serious, any more than a moderate œdema of any tissue is in itself particularly destructive to the tissue. But in the case of the kidney a complicating circumstance arises which does make such a swelling dangerous. This resides in the fact that the capsule of the kidney is not as expansible as the rest of the kidney substance. As the kidney substance swells this tends, therefore, to press upon the blood vessels and retard the circulation of the blood through the kidney. This condition actually comes to pass in the acuter forms of nephritis. The kidney already nephritic, say from the toxine of an infectious disease or an anæsthetic, tends to make itself worse by thus hampering its blood flow.

The washing out of salts from the kidney acts in the same general direction, for, as already noted, the presence of salts tends to counteract the effects of acids in producing swelling of the (hydrophilic) emulsion colloids of the kidney. Our problem might, therefore, seem to become that of balancing the good effects of water against certain bad ones. Actually the problem is much simpler. A kidney that is killing itself clearly needs water to rid itself of the poisons that are killing it and so, from this point of view, water is indicated. *We can give the kidney the benefit of these virtues of the water, while we protect it at the same time from the* *dangers associated with the water by giving along with the water certain salts.* To a consideration of this subject we will now turn.

3. The Rôle of Salts in the Relief of Nephritis.

We have labored thus far to show how a parallelism exists between the changes that various colloids undergo in the presence of any acid and the changes that are observed in the kidney when this becomes the seat of a nephritis. We have noted how the swelling of the kidney in nephritis is like the swelling of fibrin or gelatine in water when a little acid is added to this; how under the same circumstances some of the colloids go into solution, and so the development of an albuminuria is simulated; how when a colloid of the nature of casein is mixed with these, this is precipitated under conditions which make the others swell, thus behaving like certain granules observed to arise in the cells of the kidney under conditions associated with a nephritis.

In studying the behavior of the pure colloids we learned more than this. We learned, first of all, that the swelling of the colloids could be reduced, not only by neutralizing the acid, but by adding to the acid any neutral salt. So far as the precipitation of casein was concerned the salts divided themselves into two groups — the one added itself to the effect of the acid and favored precipitation, the other counteracted such an effect. If now our contention is correct that the series of changes observed in these simple colloids and in the kidney are identical in character, then it was to be expected that the *administration of properly selected salts should relieve the various signs characteristic of a nephritis.* That such is in fact the case is shown by the experiments that follow.

The choice of salts for these experiments was not an arbitrary one, and what would constitute an ideal salt for the relief of nephritis could well be told in advance. Clearly, no salt which, when employed in the concentrations and amounts necessary to get the desired effects, had any "specific" poisonous action upon the experimental animal or human being was of any use. Beyond this it was necessary to find one which combined a maximum of those effects which tended on the whole to help the nephritis (reduction of protein solubility and swelling of the kidney) with a minimum of those which aggravated such a condition (augmentation of protein precipitation in the cells). As part of the relief of a nephritis centers in the neutralization of acid, a salt capable of combining with such clearly possesses certain advantages. For this reason such salts as are the combination of a weak acid with a strong base, as the phosphates, citrates, tartrates, and malates of sodium at once suggest themselves. But neutral salts are also effective in reducing the solution and the swelling of such emulsion colloids as fibrin, gelatine, and serum albumin and so the use of the chlorides and sulphates of sodium, potassium, and magnesium suggests itself. But which of these salts may, or can in the end, be employed depends upon how urgently we wish to use them to get our effects, or how much of them we wish to give at one time, and the mode of administration employed. The citrates which, on theoretical grounds, one is tempted to use cannot be given intravenously in sufficient amounts to prove useful, though administration through the alimentary tract renders them safe. And this explains why when we come to use these salts clinically our list becomes comparatively short, and, for intravenous injection, very short indeed.

As our argument thus far has seemed to indicate to us that all the signs of a nephritis are referable to a single underlying cause, so of course we would expect that did we succeed in discovering any means of combating this cause *all* the signs of the nephritis would disappear en masse. Such is as a matter of fact the case, though to show the salutary action of the various procedures employed their effect on the various signs has been studied separately.

§ 1.

In order to show that salts inhibit the development of the signs of a nephritis it was necessary, first of all, to decide upon satisfactory methods of producing a nephritis experimentally in animals, upon which might then be tried the action of various salts. Three different methods of producing the nephritis were employed: interference with the respiration of the animal, the intravenous injection of acid, and direct clamping of the renal blood vessels. Of all these the last named is probably grossest in its effects upon the kidney. For the sake of comparison the protocols of the experiments on the animals which served as controls have been inserted in each case.

Let us turn first to a consideration of the nephritis that develops in rabbits, when these are tied into the animal holder sufficiently tight to interfere with their respiration. One always gets an albuminuria after such a procedure as the following protocols show:

Experiment 22. — White rabbit; weight 898 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter.

Time.	Urine in c.c.	Remarks.
3.00	—	Bound into holder.
3.30	3.7	Alkaline to litmus paper. No albumin.
3.45	5.0	Clearer urine. Neutral to litmus paper. Trace of *albumin*.
4.00	3.0	Clear urine. Neutral to litmus. *Albumin* present.
4.15	1.8	Clear. Neutral to litmus. *Albumin* present in every sample, and increasing in amount.
4.30	0.9	
4.45	1.1	
5.00	1.5	
5.15	1.8	
5.16		Animal seems entirely well. Returned to hutch.

Experiment 23. — Belgian hare; weight 1226 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter.

Time.	Urine in c.c.	Remarks.
2.45	Few drops	Alkaline, thick, chrome yellow. No albumin.
3.00	1.0	
3.15	0.5	
3.30	Few drops	
3.45	Few drops	Neutral and clearer. Trace of *albumin*.
4.00	Few drops	Neutral and clearer. *Albumin* present.
4.15	Few drops	
4.45	2.0	
5.00	Few drops	
5.15	Few drops	
5.16		Animal released and returned to hutch.

EXPERIMENT 24. — Belgian hare; weight 1020 grams. Fed wheat and grass. *Snugly* tied into animal holder. Urine obtained with a soft rubber catheter.

Time.	Urine in c.c.	Remarks.
3.30	3.0	Tied down. Turbid, dark yellow. Alkaline to litmus. No albumin.
3.45	0.7	
4.00	0.5	
4.15	Few drops	
4.30	2.4	Turbid, dark yellow, alkaline to litmus. No albumin.
4.45	8.5	Clearer, pale yellow. Acid to phenolphthalein. *Albumin* present.
5.00	4.0	Clear, acid to phenolphthalein. *Albumin* present.
5.15	2.0	
5.30	Few drops	
5.45	Few drops	
6.00	3.0	

EXPERIMENT 25. — Belgian hare; weight 1100 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter.

Time.	Urine in c.c.	Remarks.
4.00	1.0	Tied down. Alkaline, turbid, thick. No albumin.
4.15	2.0	
4.30	Few drops	
4.45	1.5	
5.00	2.0	Urine clear, acid to litmus. *Albumin* present.
5.15	1.5	
5.30	2.5	
5.45	3.0	
5.46		Liberated. Returned to cage.

When, now, rabbits fed the same food are treated from an experimental standpoint in an identical way but have in addition a concentrated salt solution injected intravenously, *the albuminuria does not develop.*

Experiment 26. — Black rabbit; weight 917 grams. Fed wheat and grass. *Snugly* tied into animal holder. Urine obtained with a soft rubber catheter. 105 c.c. ½ molecular NaCl solution[1] are given intravenously in the course of the experiment at the rate of 5 c.c. every five minutes.

Time.	Urine. in c.c.	Remarks.
4.00	7.5	Thick, chrome yellow, alkaline. No albumin. Injection begun.
4.15	2.5	Thick, chrome yellow, alkaline. No albumin.
4.30	7.5	Clearer. No albumin.
4.45	22.0 (?)	Clear as water. Neutral to litmus. *No albumin.*
5.00	23.0	
5.15	36.5	
5.30	32.0	
5.45	27.5	
5.46	—	Animal well. Released and killed by blow on head. Nothing abnormal noted on autopsy.

Experiment 27. — Belgian hare; weight 919 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter. 105 c.c. ½ molecular NaCl solution are injected intravenously in the course of the experiment at the rate of 5 c.c. every five minutes.

Time.	Urine in c.c.	Remarks.
3.15	4.0	Alkaline to litmus, thick, yellow. No albumin. Injection begun.
3.30	2.5	Somewhat clearer. No albumin.
3.45	20.0	Clear, colorless. Neutral to litmus. *No albumin.*
4.00	57.5	
4.15	40.0	
4.30	39.0	
4.45	29.0	
5.00	37.0	

As there is much reason to believe that a mixture of different salts when injected intravenously is less poisonous than any pure salt solution, I made the following experiments with *Ringer* solution.

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[1] That is a 2.925 per cent solution of sodium chloride.

Experiment 28. — Belgian hare; weight 901 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter. In the course of the experiment there are injected intravenously 135 c.c. of a *Ringer* solution × 4,[1] at the rate of 5 c.c. every five minutes.

Time.	Urine in c.c.	Remarks.
1.40	4.0	Turbid, alkaline to litmus. No albumin.
1.45	—	Injection into ear begun.
2.00	4.0	Turbid, alkaline to litmus. No albumin.
2.15	16.0	Clear, alkaline. *No albumin.*
2.30	38.0	
2.45	47.0	
3.00	40.5	
3.15	32.0	
3.30	13.0	Clear, neutral. *No albumin.*
3.45	7.0	
4.00	6.0	
4.05	No urine	Animal well. Returned to cage.

Experiment 29. — Belgian hare; weight 823 grams. Fed wheat and grass. Tied tightly into holder. Urine obtained with a soft rubber catheter. In the course of the experiment there are injected 125 c.c. of a *Ringer* solution × 4, at the rate of 5 c.c. every five minutes.

Time.	Urine in c.c.	Remarks.
1.50	—	Tied down.
1.55	—	Injection into ear begun.
2.10	—	
2.25	3.0	Turbid, alkaline. *No albumin.*
2.40	18.0	Clear, alkaline. *No albumin.*
2.55	13.0	Clear, neutral to litmus. *No albumin.*
3.10	17.0	
3.25	20.0	
3.40	8.0	
3.55	4.0	
4.00		Dies. Nothing abnormal noted on autopsy.

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[1] The sodium, potassium, calcium chloride mixtures that are known as *Ringer* solutions have a different composition with different authors. I used the following: NaCl 0.7, $CaCl_2$ 0.0026, KCl 0.035, and H_2O enough to make 100 c.c. *Ringer* solution × 4 means four times this amount of salts in each 100 c.c., a solution which has then about the same osmotic concentration as a ½ molecular NaCl solution, as used in the previous experiments.

Experiment 30. — Belgian hare; weight 855 grams. Fed wheat and grass. Tied tightly into holder. Urine obtained with a soft rubber catheter. In the course of the experiment there are injected 150 c.c. of a *Ringer* solution × 4, at the rate of 5 c.c. every five minutes.

Time.	Urine in c.c.	Remarks.
2.30	1.0	Turbid, alkaline. No albumin. Tied down and intravenous injection into ear begun.
2.45	1.7	Urine clears until it looks like water. *No albumin* at any time.
3.00	3.6	
3.15	11.0	
3.30	12.5	
3.45	21.0	
4.00	25.0	
4.15	23.0	
4.30	25.0(?)	Clear, acid. *No albumin* at any time.
4.45	9.5	
5.00	12.5	
5.15	10.0	
5.20	...	Killed. On autopsy nothing abnormal except that 25 c.c. fluid are obtained from the peritoneal cavity!

Our interest in these experiments has thus far centered in the development and the nondevelopment of an albuminuria. Let us now retrace our steps and see what has happened so far as urinary secretion is concerned, for we were rather particular to emphasize the fact that the ability of the kidney to secrete water was perhaps the best index of its functional activity. What we are interested in knowing is concerned with a problem of immediate practical worth. *Can the secretion of urine from a nephritic kidney, or one threatened with a nephritis, be maintained at a normal level or be increased by the giving of various salts?*

The experiments detailed above already suffice to answer this in the affirmative, and let it be noted that this holds true even in the case of sodium chloride which in recent years has been particularly warmly criticised, it having even been maintained by not a few authors that this particular salt is responsible for the water retention in nephritis (and in certain other diseases associated with œdema). That such a belief is unwarranted is proved as soon as we compare with each other Figs. 23, 24, and 25, and Experiments 22, 23, 24, 25, 26, 27, 28, 29, and 30, upon which these are based. All the figures are drawn to the same scale (though they have not been reproduced on the same scale). The rate of urinary secretion is indicated in number of cubic centimeters obtained in each 15 minutes.

Figure 22 shows normal urinary secretion in three rabbits that were loosely tied into an animal holder. The curves *a*, *b*, *c*, and *d* of Fig. 23 (based respectively on Experiments 25, 22, 24, and 23) show, when compared with the curves of Fig. 22, how the secretion of urine is diminished when, instead of being loosely tied into the animal holder, the rabbits

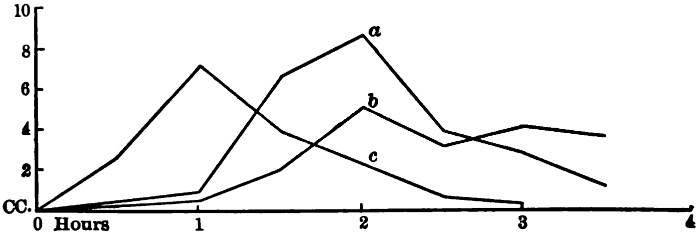

FIG. 22.

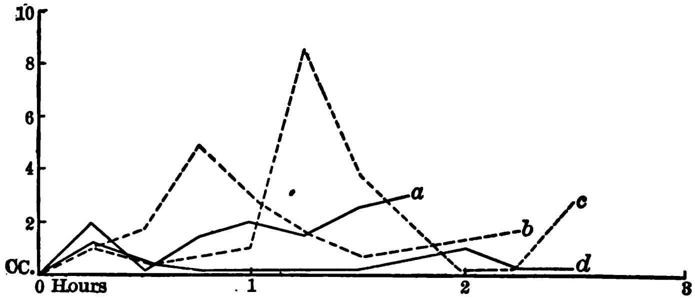

FIG. 23.

are so snugly tied down as to embarrass their respiration. *The diminished secretion gives way to an enormously heightened one if animals similarly treated are injected with a concentrated sodium chloride solution.* Figure 24, drawn to the same scale as Fig. 23, shows this very well. The curve *a* is taken from Experiment 27, curve *b* from Experiment 26. These experiments (as others to be described directly) show very well that sodium chloride does *not* lead to a retention of water by the living animal.

Let us now look at Fig. 25 which shows the curves obtained by injecting concentrated *Ringer* solution. Evidently all salts (that have not specific poisonous effects) if injected in sufficient concentrations increase the output of urine. The curves *a*, *b*, and *c* are constructed respectively from Experiments 28, 29, and 30. As noted in the protocols the rabbits were again snugly tied into animal holders, but not only did none of them develop an albuminuria but, in consequence of the injection of the concentrated *Ringer* solution, the urinary output was enormously increased in all.

§ 2.

We will now consider a second method of inducing a nephritis, namely, through the injection of acid into an animal, and see if our concentrated sodium chloride is again able to prevent or relieve the signs of a nephritis as thus induced. As the following experiment shows, *sodium chloride when injected intravenously, in concentrated solution, simultaneously with a hydrochloric acid solution of a concentration which we found in Experiments* 13 *and* 14 (*pages* 38 *and* 39) *to lead to the symptoms of a most intense acute nephritis, practically suppresses this entirely. The albuminuria scarcely appears, and there are no casts, no red blood corpuscles, no hæmoglobinuria, no decrease in the amount of urinary secretion, and no general œdema.*

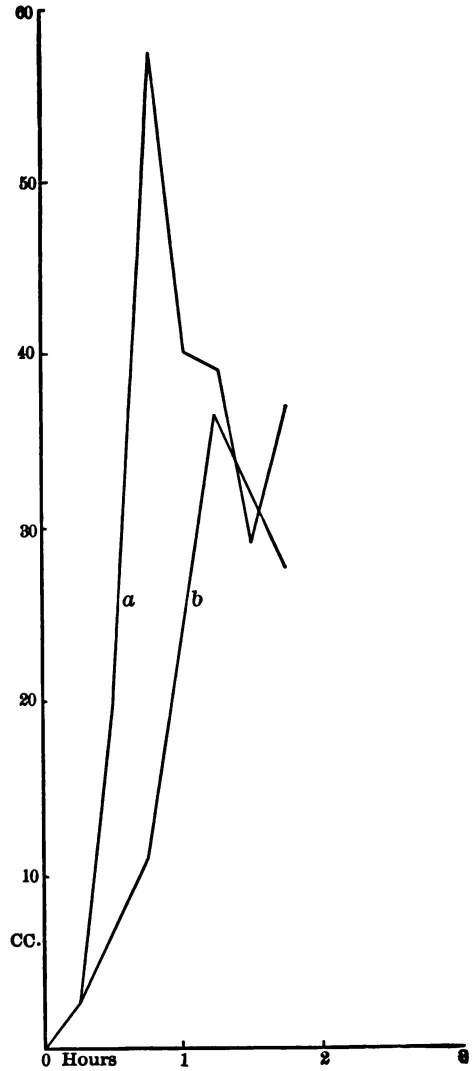

FIG. 24.

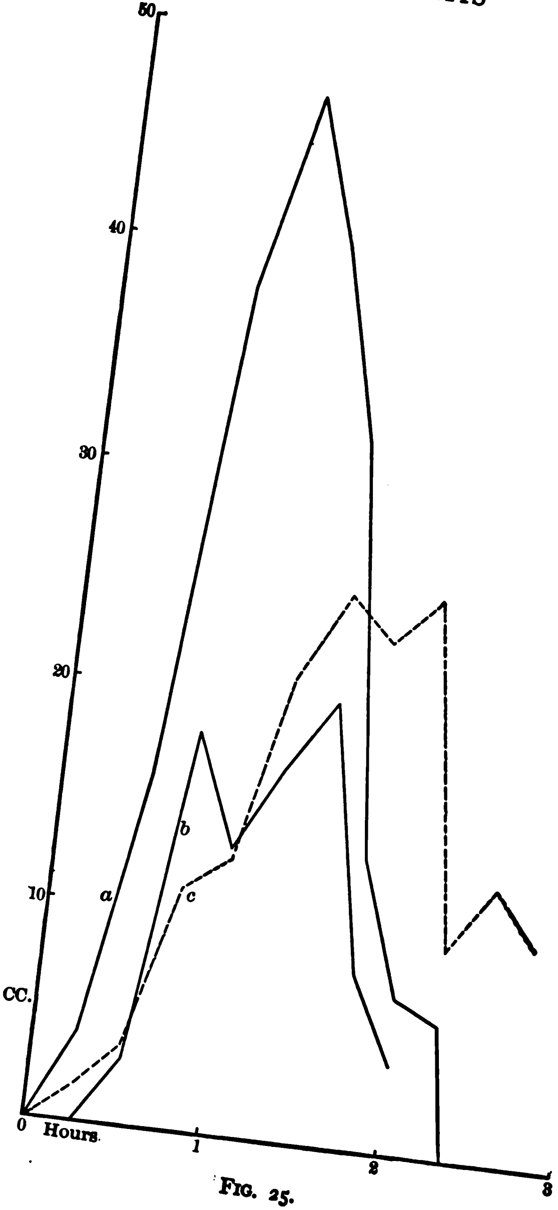

FIG. 25.

Experiment 31. — Belgian hare; weight 2136 grams. Has been fed hay, oats, corn, and greens. In the course of the experiment there are injected intravenously at a uniform rate 140 c.c. of the following mixture: 150 c.c. $\frac{1}{10}$ normal HCl plus 4.666 grams sodium chloride and enough water to make the whole up to 160 c.c. This yields a final solution that is $\frac{1}{2}$ molecular so far as the sodium chloride is concerned. Urine obtained with a catheter.

Time.	Urine in c.c.	Remarks.
3.30	—	Catheterized. Weighed and fastened to animal board.
3.45	—	Injection into ear begun.
4.00	0.3	Slightly turbid, neutral to litmus paper. No albumin. No casts.
4.15	17.0	Clear as water, barely reddens blue litmus paper. No albumin. No casts.
4.30	61.0	Clear, barely affects blue litmus paper. Faint shimmer of albumin! No casts!
4.45	64.5	Urine clear, barely affects blue litmus paper. Faint trace of albumin. No casts. No hæmoglobinuria at any time. No red blood corpuscles in the urine.
5.00	58.0	
5.15	38.0	
5.18	1.0	Dies.

Total amount of urine secreted since beginning injection 239.8 c.c. *Autopsy.* Weight 2035 grams! Nothing abnormal is noted. The body cavities contain no fluid. The blood seems to coagulate abnormally rapidly.

It might be insisted in criticism of this experiment, that while sodium chloride is thus able to counteract the effects of an acid in producing a nephritis, it cannot relieve such after once being established. This criticism is met in the following Experiment 32, in which a nephritis is first induced by injecting (practically) pure acid, after which its relief is brought about by injecting $\frac{1}{2}$ molecular sodium chloride.

Experiment 32. — Belgian hare; weight 2343 grams. Fed hay, oats, corn and greens. Urine obtained with a soft rubber catheter. In the course of the first $1\frac{1}{4}$ hours of the experiment there are injected at a uniform rate 125 c.c. of the following mixture: 120 c.c. $\frac{1}{10}$ normal

HCl plus 8 c.c. $\frac{2}{1}$ molecular NaCl, in consequence of which all the signs of a nephritis develop. For the acid mixture is then substituted a pure $\frac{1}{2}$ molecular NaCl solution of which, up to the end of the experiment, there are injected 125 c.c. Coincident with this change in the character of the injection fluid all the signs of the nephritis are seen to disappear.

Time.	Urine in cubic centimeters.	Remarks.
2.45	5.0	Catheterized. Turbid, light yellow, faintly alkaline to litmus paper. No albumin. No casts.
3.00	1.5	Weighed. Tied to animal holder. Intravenous *injection of acid mixture into ear begun.* Urine turbid, light yellow, faintly alkaline to litmus paper. No albumin. No casts.
3.15	0.7	Urine neutral to litmus paper. No albumin. No casts.
3.30	—	
3.45	2.1	Urine neutral to litmus paper. No albumin. No casts.
4.00	10.0	Urine faintly acid. Albumin. Isolated casts. Epithelial cells and red blood corpuscles.
4.15	7.0	Urine has a pink tinge. More albumin. Numerous casts and a larger number of red blood corpuscles. Injection of acid mixture stopped. *Injection of $\frac{1}{2}$ molecular NaCl begun.*
4.30	20.0	Urine decidedly red (hæmoglobinuria). Albumin content still rising. Fewer casts and red blood corpuscles.
4.45	42.0	Pink color to urine. Albumin decreasing. No casts can be found after long search of sedimented urine.
5.00	60.0	Pale pink. Albumin decreasing. No casts or red blood corpuscles.
5.15	53.0	Like water. Barely visible trace of albumin. No casts or blood corpuscles.
5.30	32.0	Like water and neutral to litmus paper. No albumin. No casts. No blood cells. *Injection stopped,* as animal has embarrassed respiration.
5.35	11.0(?)	Some urine accidentally lost as animal dies. No albumin. No casts. No blood cells.

Autopsy. — Weight 2342 grams. Nothing abnormal in any of the organs. The peritoneal cavity is wetter than normal. The pericardial and pleural cavities are empty.

A number of interesting facts come to light in the two experiments just detailed. Let us first ask about the output of urine. In Fig. 26 we find in the curves *a* and *b* (Experiments 13 and 14) a graphic representation of the amount of urine secreted when a $\frac{1}{10}$ normal hydrochloric acid solution (in $\frac{1}{8}$ molecular, that is 0.733 per cent sodium chloride, added to reduce somewhat the hæmolytic action of the acid) is injected intravenously. When we compare these curves with those of Fig. 22 (normal secretion in rabbits), we notice that in spite of the great injection of water, the urinary output lies below the normal. The presence of the acid along with the water brings it to pass that the water is retained in the body; in other words, an œdema develops. The same factor, therefore, which we are holding responsible for certain of the kidney changes in nephritis, is responsible for one of the most prominent symptoms of such kidney disease, namely, the œdema.

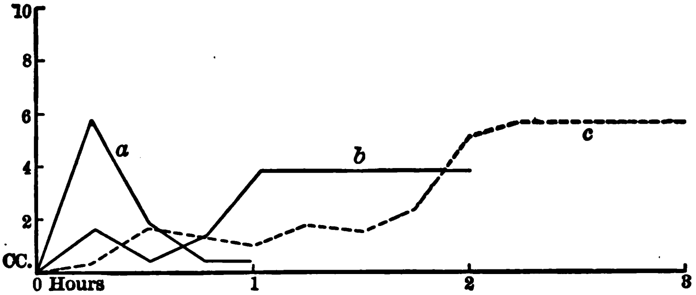

FIG. 26.

How enormously the urinary output is increased if a concentrated sodium chloride solution is injected along with the hydrochloric acid is apparent when Fig. 27, drawn to the same scale, is compared with Fig. 26. And when we look through the protocols we find that this increased urinary output is associated with a loss of weight by the animal, in other words, a failure to develop an œdema, or the reduction or total disappearance of such as may be existing.

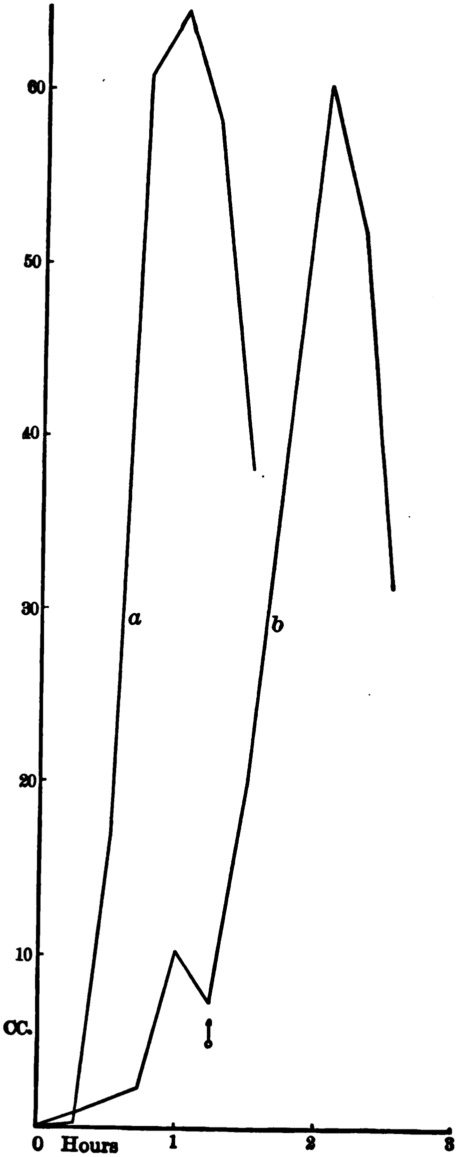

FIG. 27.

Clearly, therefore, salts, including sodium chloride, all tend to reduce œdema, as I have previously insisted.

Another point of interest in these two experiments is the fact that when enough sodium chloride is injected along with the acid, the hæmoglobinuria fails to develop. As is well known a pure acid solution when injected intravenously leads to a rapid and extensive destruction of the red blood corpuscles (hæmolysis) and the escape of hæmoglobin in the urine. The only reason why *some* sodium chloride was given along with the acid injections in the various experiments described in this volume, in which the effects of the pure acid on the kidney were particularly sought, was to escape in part this so great dissolution of the red blood corpuscles. When enough sodium chloride is added the hæmolytic action of the acid is avoided altogether, as Experiment 31 shows. This fact is of interest and importance not only because it teaches us that by increasing the salts in the diet we can relieve the signs and symptoms of paroxysmal hæmoglobinuria,[1] but because it was a result to be expected if a theory of hæmolysis which I have previously advanced[2] should be correct.

Incidentally, these last two experiments in conjunction with Experiments 12, 13 and 14 (pages 37 to 39) serve to meet a criticism that might have been raised against our experiments on asphyxia nephritis, in which it might have been said that the great urinary secretion obtained after injecting salt solutions was due *merely* to the injection of so much water.

§ 3.

As *Max Herrmann* first showed, direct interference with the blood supply to the kidney leads to very destructive changes in this organ in an incredibly short space of time

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[1] *Oscar Berghausen:* Unpublished paper.

[2] *Martin H. Fischer:* Kolloid Zeitschr. **5**, 146 (1909) and Œdema, 166, New York, 1910.

— the output of urine falls or may be stopped entirely and albumin, casts, and blood are found in such as is secreted. If the kidneys are examined these are found to be swollen, maybe grayish, and to present varying degrees of hæmorrhage into the kidney substance. The following experiment illustrates this.

Experiment 33. — Belgian hare; weight 2335 grams. Fed hay, oats, corn, and greens. Urine obtained with a catheter. The right renal artery and vein, and the left renal artery are clamped for one-half hour.

Time.	Urine in c.c.	Remarks.
2.05	—	0.008 gram morphine hydrochloride given subcutaneously.
2.15	15.0	Clear, brownish yellow, faintly acid to litmus. No albumin. No casts. After catheterizing the animal is weighed.
2.50	—	Tied into holder.
3.00	0.5	Right renal artery and vein and left renal artery are clamped.
3.15	—	
3.30	—	Clamps removed.
3.45	—	
4.00	—	
4.15	1.0	Much albumin. Hyaline casts and red blood corpuscles.
4.30	—	
4.45	0.5	Thick, turbid, acid to litmus. Full of albumin and casts.
5.00	0.8	
5.15	—	
5.30	0.8	Thick, turbid, acid to litmus. Full of albumin and casts.
5.31	—	Animal appears well, is killed.

Autopsy. — Kidneys are swollen and deep red, but otherwise show nothing strikingly abnormal to the naked eye.

The urinary output in this experiment is illustrated in curve *c* of Fig. 28. Let us now see how an animal similarly treated fares if it receives an intravenous injection of a "physiological," ⅛ molecular (0.733 per cent) sodium chlo-

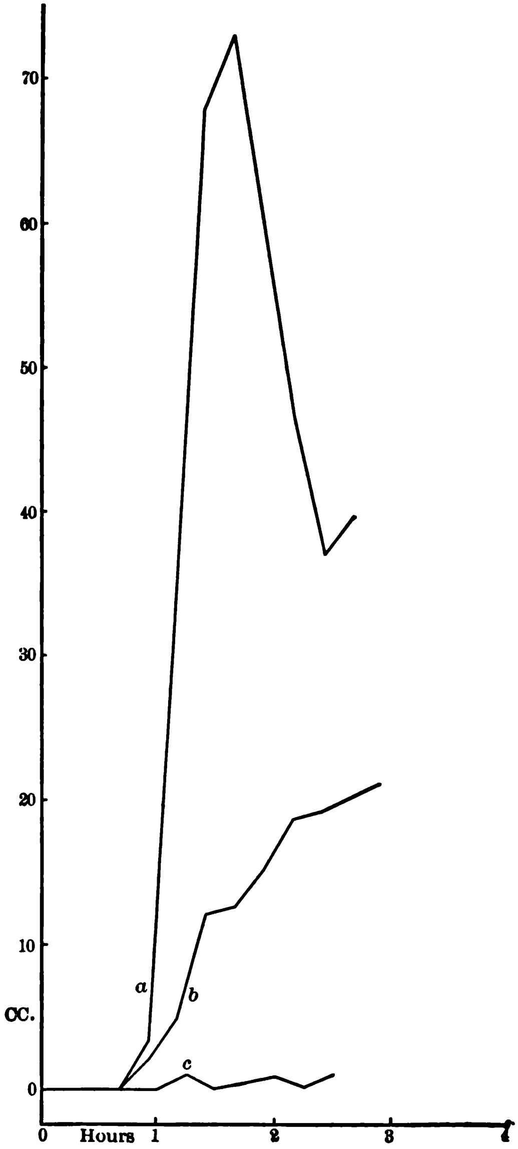

Fig. 28.

ride solution. Such an experiment serves to answer two very important questions. First, is the giving of water to a case of "acute nephritis" dangerous because it "throws work on the kidney" and we need to "protect" this organ against doing any work; and second, does the administration of sodium chloride aggravate such a nephritis because,

Experiment 34. — Belgian hare; weight 2184 grams. Fed hay, oats, corn, and greens. Urine obtained with a catheter. The right renal artery and vein, and the left renal artery are clamped for one-half hour. Thereafter, 215 c.c. of a ⅛ molecular NaCl solution are injected at a uniform rate intravenously.

Time.	Urine in c.c.	Remarks.
11.20	—	0.016 gram morphine hydrochloride given subcutaneously.
11.40	2.0	Thick, yellow, turbid, acid to rosolic acid. No albumin. No casts. Catheterized and weighed.
12.10	2.0	Same. Right renal artery and vein and left renal artery clamped.
12.25	—	
12.40	—	Clamps removed.
12.50	—	Injection of ⅛ molecular NaCl into ear begun. Accident to needle interrupts injection for 10 minutes.
1.05	2.0	Full of albumin, epithelial, finely granular, and hyaline casts.
1.20	4.7	Acid to rosolic acid. Full of albumin, epithelial, finely granular, and hyaline casts.
1.35	12.0	Clear as water. Albumin going down. It is noted that there is decidedly more albumin in this experiment than when ⅙ molecular NaCl is used, volume of urine duly considered.
1.50	12.5	Decided drop in albumin. Still some casts.
2.05	15.0	Clear as water. Albumin present in traces only. Occasional cast only.
2.20	18.5	Same. Trace of albumin visible after standing.
2.35	19.0	No albumin. No casts.
2.50	20.0	
3.05	21.0	
3.06	—	Killed.

Autopsy. Weight 2269 grams. 6.0 c.c. fluid in peritoneum. Pleural and pericardial cavities dry. Nothing abnormal noted in any organ.

as some say, it "further increases the work of the kidney" or because it "irritates" this organ? A no inconsiderable portion of the therapeutic world to-day insists on both restriction of water and of sodium chloride in cases of acute nephritis. That both should be given and that the sodium chloride, far from adding itself as a factor of evil to the water, really counteracts the only bad effects this might have (through favoring the swelling of the kidney and washing out salts) is shown by the results of the Experiment 34.

The increased urinary output, in consequence of the injection of the $\frac{1}{8}$ molecular sodium chloride solution, is clearly evident when curve *b* of Fig. 28, based on this experiment, is compared with the curve *c* as obtained in the previously described Experiment 33. We note, moreover, that with the concentration of sodium chloride employed in Experiment 34 a not inconsiderable amount of the injected water is retained, in other words, the animal develops an *œdema.* In the terms of the osmotic theory of water absorption (which we do not accept) this would be explained by saying that a 0.733 per cent sodium chloride solution has a lower osmotic concentration than the body fluids of the rabbit. Many clinicians who believe that sodium chloride "leads to œdema" might be inclined to say that this experiment supports their contention. That it does not is shown by the following Experiment 35 in which an animal, again rendered nephritic by clamping the renal vessels, is again injected with the same amount of water at the same rate, but the concentration of the sodium chloride is further increased (to $\frac{1}{2}$ molecular NaCl, that is 2.918 per cent). As the protocol and curve *a* of Fig. 28 show, the urinary output under such circumstances is still further, really enormously increased, and also not only does no œdema develop, but the animal actually loses in weight.

To the interpretation of these various findings, which it was entirely possible to predict, we shall come immediately.

Experiment 35. — Black rabbit; weight 2778 grams. Fed hay, oats, corn, and greens. Urine obtained with a catheter. The right renal artery and vein, and the left renal artery were clamped for one-half hour. Thereafter, the animal received at a uniform rate an intravenous injection of 170 c.c. ½ molecular sodium chloride solution.

Time.	Urine in c.c.	Remarks.
1.55	—	0.016 gram morphine hydrochloride are given subcutaneously.
2.20	14.0	Yellow, turbid, alkaline to litmus. No albumin. No casts. After catheterizing the animal is weighed.
2.45	2.3	Yellow, clear, alkaline. No albumin. No casts. Right renal artery and vein, and left renal artery are clamped.
3.00	—	
3.15	—	Clamps removed.
3.25	—	Intravenous injection of ½ molecular NaCl begun.
3.40	3.5	Filled with casts and red blood corpuscles. Fairly sets with albumin.
3.55	32.5	Last portions clear as water.
4.10	68.0	Clear as water. Acid to phenolphthalein, alkaline to rosolic acid. Faintest trace of albumin only. No casts. Occasional red blood corpuscles.
4.25	73.0	
4.40	59.0	
4.55	46.5	
5.10	37.0	
5.25	39.5	
5.26	?	Animal killed. Approximately 10 c.c. urine lost in interval between stopping injection and making autopsy.

Autopsy. — Weight 2554 grams! 19.0 c.c. fluid found in peritoneal cavity. Pleural and pericardial cavities are dry. Kidneys are slightly grayish.

The following Experiment 36 shows for what a long period the blood supply to the kidney may be cut off and yet the dangers ordinarily incident to such a procedure (partial to complete suppression of urine) be reduced by giving a concentrated salt solution. The experiment was really undertaken to indicate how the so-feared consequences of temporary occlusion of the blood vessels in operations on the kidney may be largely avoided — a discussion to which we shall return immediately.

EXPERIMENT 36. — White and blue rabbit; weight 2344 grams. Fed hay, oats, corn, and greens. Urine obtained with a catheter. The right renal artery and vein and the left renal artery and vein are clamped for 1½ hours. After an interval, 90 c.c. ½ molecular NaCl solution are injected at a uniform rate intravenously.

Time.	Urine in c.c.	Remarks.
9.20	—	0.016 gram morphine hydrochloride are given subcutaneously.
9.50	—	Tied down.
10.05	1.3	Deep brownish-yellow. No albumin. No casts. Renal blood vessels are clamped.
10.20	—	
10.35	—	
10.50	—	
11.05	—	
11.20	—	
11.35	—	Clamps removed.
11.50	—	
12.05	—	
12.20	—	
12.35	—	
12.50	—	
1.05	—	
1.20	—	
1.35	—	
1.55	—	*Injection of ½ molecular NaCl into ear begun.*
2.10	—	
2.25	0.3	Filled with albumin and hyaline casts (exclusively).
2.40	0.4	
2.55	0.4	
3.10	0.8	
		Injection stopped.
3.25	2.6	Urine clearer. Filled with hyaline and granular casts.
3.40	2.8	Casts fewer.
3.55	1.5	No casts.
3.55 to 5.25	11.3	No casts. Red blood corpuscles found (traumatic).
5.40	1.5	No casts.
5.41	—	Killed.

Autopsy. — Weight 2300 grams. 10 c.c. fluid in peritoneal cavity. 1.2 c.c. in right pleural cavity. Left unusually moist. Kidneys soft and somewhat gray.

The secretion of urine in this experiment is represented graphically in Fig. 29. The first arrow indicates the point in the experiment when the clamps were removed. Up to point of the second arrow no urine was obtained. At this time the sodium chloride injection was started. The secretion of urine began less than half an hour afterwards.

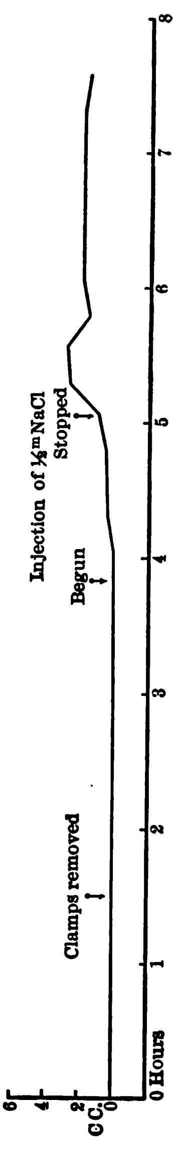

FIG. 29.

§ 4.

It behooves us now to pause for a moment and to study the just described experiments in order to discover the *principles* that underlie the results obtained, for only by knowing these can we hope to put them to any intelligent therapeutic use. In the light of the ideas developed in this volume, and my remarks on urinary secretion[1] the following seems to me safe ground.

The living organism represents in the resting state a series of colloids which are saturated with water. The blood and lymph constitute an integral part of this system. No water can be absorbed by the living organism, and none be given off except as conditions are first offered in the body as a whole or locally (individual organs or cells), which increase or decrease this normal relationship between the colloids and the water bound to them. As in our discussion of the kidney we are dealing with the problem of secretion, we can at once recall to mind experimental and clinical evidence to support such a view by remembering that in absolute starvation urinary secretion ceases (practically) entirely. And so we are not surprised to find that the urinary output of a normal rabbit shortly after we stop feeding it shows signs of diminution and soon thereafter signs of complete cessation (Fig. 22). From this we can immediately learn a practical point that is ignored medically all too often, and that is that *the only way to increase the urinary output is to give water*, and (if we ignore the skin and respiration) we can say that we increase this in proportion to the amount of water given. Many if not all of *the diuretics act in the same way. They are diuretics only because they make for conditions in the body which decrease the avidity with which the colloids of the body are holding on to their water.*

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[1] *Martin H. Fischer:* Œdema, 180. New York, 1910. See also Kolloidchemische Beihefte, **2**, 304 (1911).

Let us see now what happens when we tie our otherwise normal rabbit so snugly into an animal holder that we interfere with its easy respiration. That the urinary output falls under such circumstances is shown in Fig. 23. What happens here is this: we favor under these circumstances the accumulation of carbon dioxide and other acids in his body. This raises the avidity with which the colloids of all the tissues of the body hold on to their water, and so none is left over to be secreted as urine. The animal is, in other words, at once put into a condition similar to that attained after several hours by the animal simply kept off of food and water. In addition to any local acid effect we may have in the kidney (swelling of the kidney, etc.), we have also in this case an acid effect upon all the tissues of the body. Not only therefore is the kidney placed in a position in which it cannot secrete as well as normally, but the material necessary for this secretion (water) is also withheld. Parenthetically we may add that a state similar to that induced here by tying the animal down is obtained when we give a dose of morphine, cocaine, atropine, arsenic, an anæsthetic like chloroform or ether, an excessive dose of alcohol, or a nitrite.

Essentially the same state of affairs is produced if we inject an acid solution intravenously. The acid acts upon the tissue colloids, increases their affinity for water, and these therefore absorb and hold on to all that is given them in these experiments along with the acid. And so we have again none left over to be secreted by the kidney. The animal retains the water, increases in weight; it develops an "œdema." This general effect of the acid on the body as a whole, adds itself therefore to the acid changes that occur in the kidney itself under such circumstances. The acid circulating in the kidney makes the cells here swell. This compresses the blood vessels of the kidney, and so the state of the kidney becomes still more precarious. To its already serious acid state the kidney adds further danger by reducing its own blood supply (which means a further formation and accumulation of acid in the kidney), and so a vicious circle is established.

Let us consider, first of all, what must happen if we give pure water to such an animal. Its effects are in part good, in part bad. Very evidently only by giving water can we hope to get the body colloids generally once more saturated with water and so get some left over for a urinary secretion, and only as we get a urinary secretion can we hope to wash out the acids (and other toxic substances) that are killing the kidney cells. And this holds, as we shall see, even when we deal with a case of generalized œdema. The only bad effects of giving water reside in favoring the swelling of the kidney. But this feature we can avoid, as we have said before, by giving salts.

To the relief of all the conditions that characterize our picture of nephritis comes the administration of salt (along with the water). The salts — including sodium chloride — reduce the amount of water that can be held by the body colloids generally, and so this freed water now becomes available for urine. The kidney itself shares in this process and by shrinking admits a better circulation to be once more established through it. In this way everything tends to be reëstablished in a normal way once more. The body now loses water, and so the animal weight, in other words the œdema disappears again. Under the same circumstances the kidney proteins become less soluble and so the albuminuria goes. The disappearance of the casts is peculiarly interesting. Immediately following a salt injection the number of casts seems increased. We note, moreover, that they are smaller, and while hyaline casts may have predominated before, granular ones now fill the field. The sudden apparent increase in the number of casts is due to the shrinkage under the influence of the increased salt concentration of the casts as they lie in the kidney tubules, and so their easier and sudden washing out from these tubules by the increased urinary flow obtained under the same circumstances. The granular casts represent the reconversions of the hyaline casts back into the granular under the influence of the salt.

§ 5.

We come now to the highly important matter of applying what has been found to hold in animals to human cases. The credit of having been the first to adapt the principles outlined in this volume to clinical cases belongs to *James J. Hogan*. An abstract of his first two cases follows. Since then others of my friends and colleagues have used alkalies, salts, and water for the relief particularly of the acuter nephritides, and with favorable results. My thanks are due all these for permitting me to use the facts that are contained in the following brief outlines of their cases.

The entire purpose of our therapy must be to get alkali into our patient in order to neutralize the acids present; to get salt into him to aid in the reduction of the œdema of the kidney (and other organs); and finally, to give him water in large doses at regular intervals in order to have "free" water available for urine. How we may accomplish our ends by administering these by mouth, or in the acuter cases by giving properly concentrated solutions of sodium carbonate and sodium chloride by rectum or intravenously is indicated in the abstracts.

CASE I.— (*Dr. James J. Hogan*, Vallejo, California.) Mrs. R., pregnant and practically at term, entered the hospital March 7, at 5.30 P.M., complaining of continuous uterine pain. The patient had a general œdema. Signs and symptoms indicating that a nephritis had existed for at least some days past were evident, but no proper examination of the urine had been made. The os on examination was found rigid. Because of the intense pain 0.015 gram morphine was given hypodermically at 9.00 P.M. She went to sleep but awoke at 11.00 in a severe convulsion. The patient was catheterized and 60 c.c. of bloody urine of a syrupy consistency were obtained. On testing this for albumin it fairly set. Casts, cellular detritus, red blood cells, etc., were found microscopically. 600 c.c. of an 0.85 per cent sodium chloride solution were given by rectum and immediate emptying of the uterus was deemed necessary. This was done under ether anæsthesia and as the os was very rigid required a half hour. A second convulsion occurred on the operating table. Immediately after the operation another 500 c.c. of an 0.85 per cent sodium chloride solution were given by rectum. Between this time (11.30 P.M., March 7) and 4.50 P.M., March 11, in other words, for practically four days, no urine could be obtained by catheter. During this time no convulsions occurred and the patient's mind remained clear. A continuous salt drip was used in the rectum and water and magnesium sulphate were given by mouth, but no evidence of a return of urinary function was obtainable. It was now decided to use a more concentrated sodium chloride solution and alkali. The following mixture was therefore prepared.

Sodium carbonate (crystallized)[1] . .	20 grams
Sodium chloride	14 grams
Water enough to make	1000 c.c.

This was injected into the rectum at body temperature by a continuous drip method. In an hour and ten minutes 30 c.c. of bloody urine were obtained, and an hour later 80 c.c. more. From now on the urine fairly streamed out. The secretion continued and the albumin and casts entirely disappeared from the urine by the fourth day. The patient made an uninterrupted recovery.

CASE 2.— (*Dr. James J. Hogan*, Vallejo, California.) Mrs. W., 22 years old. *Dr. Hogan* was called in consultation on the evening of March 11, and found the patient unconscious with practically complete suppression of the urine that had lasted for twenty-four hours. The unconsciousness had lasted for twelve hours. The nephritis in this case was secondary to scarlet fever. The formula used in Case 1 was given by the continuous drip method per rectum. The urinary flow recommenced after four hours; on the following day her mind had cleared, and the patient made a subsequent uneventful recovery.

CASE 3.— (*Dr. H. Kennon Dunham*, Cincinnati.) Master M., 7 years old, was seen on April 30, 1911, by *Dr. Wm. C. Schmidter* in a rather mild attack of scarlet fever. The temperature at no time ran above 101° F. In spite of the apparent mildness of the attack, the child developed urinary symptoms. On May 7, when *Dr. Dunham* was first summoned in consultation, a complete suppression of urine had lasted for fifty-one hours, the child was conscious, but very stupid, presenting a grave picture of intoxication. The eyelids and ankles were swollen, the pulse 105, respiration 24.

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[1] When the crystallized sodium carbonate is not at hand, and only the ordinary dried preparation is available, *only about one third of this must be employed*, for approximately two thirds of the crystallized substance is water of crystallization.

At 4.00 A.M. the following mixture was prepared and its injection into the rectum begun:

Sodium chloride	30 grams
Sodium carbonate (crystallized) . . .	20 grams
Water	1000 c.c.

The injection required one and a half hours. About 180 c.c. were rejected, the remainder of the above solution was retained. Three and a half hours after the injection was completed the patient passed involuntarily a large watery stool. Ten hours after the completion of the injection he passed a small amount of highly colored urine. Following this at short intervals came large voidings of urine which were lost into the bed as the child could not control himself sufficiently to use a bedpan. Not until this secretion had lasted for four hours could the urine be collected. Not counting that which was lost there were collected 2272 c.c. of urine in the first twenty-four hours after urinary secretion commenced. The first specimens of urine obtained were so filled with albumin as to set into a solid mass on boiling. The amount of albumin rapidly decreased in amount, so that during the second day after the injection only a moderate reaction for albumin was obtained, and on the ninth day it disappeared entirely. The intense stupor left the child within the first twenty-four hours after injection, and on the third day he was actively interested in his surroundings and free from œdema. His urinary secretion after being started was readily maintained by the milk diet on which he had been from the first and to which alkaline mineral water was added ad libitum.

CASE 4. — (*Dr. Lemuel P. Adams*, Oakland, California.) Mrs. E., 26 years old and a primipara, began to feel below par, became pale, and developed a generalized œdema when pregnant seven and a half months. The secretion of urine was low, and this contained much albumin and various casts. Her condition gradually grew worse, so that it was deemed wise to put her to bed in the hospital. For ten days, here on a milk diet, and cared for in the approved ways, she showed no improvement, passing between 240 and 360 c.c. of urine per twenty-four hours, filled with albumin, casts, and red and white blood corpuscles. As she now began to develop twitchings, was extremely œdematous and nearly blind, and as the onset of convulsions was feared, premature labor (at 8 months) was induced through gradual dilatation of the uterine os by means of water bags. Complete suppression of urine followed delivery. After this had lasted for thirty-one hours and no urine had come consequent upon hot packs, cupping, digitalis, etc., a slow injection of the following mixture into the rectum was begun:

Sodium chloride	14 grams
Sodium carbonate (crystallized) . . .	20 grams
Water	1000 c.c.

Urine began to come four hours after the injection was commenced and amounted to 1536 c.c. in the first twenty-four hours. Two injections daily of 500 c.c. each of the above formula were continued for three days, together with water, milk, and cereals by mouth. On the second day 2176 c.c. of urine were obtained, on the third 2140, on the fourth 2180, and on the fifth 1856. On the fifth day casts and blood cells had entirely disappeared from the urine and only the faintest trace of albumin remained. The œdema had diminished greatly, eyesight was returning, and the patient was actively interested in her surroundings. On the following day the last of the albumin was gone and the patient went on to an uneventful recovery.

CASE 5. — (*Drs. Otto P. Geier* and *J. L. Tuechter*, Cincinnati.) G. L., a 34-year-old attorney, developed a severe tonsillitis involving both tonsils on May 17, 1911. His temperature was 103.5° F., pulse 120. The urine was very scanty, high colored, and contained albumin and casts. The next day the patient had intense headache, and in the evening became delirious. During these second twenty-four hours of his illness he passed but 90 c.c. of urine, very smoky in color and filled with albumin, red and white corpuscles and casts of all sorts. On the third day of his illness he passed no urine at all. His delirium continued and his temperature remained at 103° F., his pulse at 124. Late at night he was given the following mixture per rectum:

Sodium chloride	14 grams
Sodium carbonate (crystallized). . .	20 grams
Water	1000 c.c.

In his delirium most of this first injection was rejected. At 3.00 A.M., May 20, the injection was therefore repeated. About 500 c.c. of the formula were retained. At 6.00 A.M. 150 c.c. of dark, thick urine were obtained, which on heating fairly set into a jelly. The urinary secretion became more profuse as the day wore on, and in the first twenty-four hours after the successful injection 1184 c.c. of urine were obtained. As the urinary secretion increased, the drowsy delirium passed away, the headache disappeared, and the patient volunteered that he felt well. The temperature fell to 101° F., the pulse rate to 100. The later specimens of urine voided in these twenty-four hours after the successful injection were clear and amber in color and contained only a little albumin, and few casts and blood cells. The rectal injections of 500 c.c. of the above formula were repeated May 21 (temperature 99.5° F., pulse 90) and May 22 (temperature normal, pulse 70), and the patient was urged to take as much Vichy water by mouth as he could. The urine secreted May 21 measured 1376 c.c., that secreted May 22, 1408 c.c. Some albumin and casts were found in the former, only a trace together with some red blood corpuscles but no casts in the latter. On May 23 all urinary signs had disappeared, and the patient made an uneventful recovery.

CASE 6. — (*Dr. Dudley Smith*, Oakland, California.) Mrs. W., aged 30, and seven months pregnant, presented herself for examination in May, 1911, with a history of nephritis and threatened eclampsia in her first pregnancy, ten years before. The second pregnancy three years before had been uneventful. Urinary examination when the patient first presented herself was negative. On June 7, she began to show albumin in her urine and marked signs of general intoxication. Œdema of the face and feet developed. She was put to bed and placed on a milk diet, and saline cathartics were administered. Under this treatment she got no better. About the first of July, active administration of alkalies was begun in the form of one to one and a half grams of sodium carbonate dissolved in a glass of plain water, or Vichy water, every two hours. Marked and positive improvement occurred in all her general symptoms and the œdema disappeared entirely. She was permitted to get out of bed again, but the alkali therapy was continued. On this regime she was carried to full term with no further general symptoms of consequence. Her urinary output lay between 1800 and 2800 c.c. daily and some albumin and casts continued in the urine. On July 24 she complained of severe continuous uterine pain, and with this came a marked reduction in the urinary output, extreme nervousness, and severe headache with nausea and vomiting. On the morning of July 25 the urinary secretion had stopped entirely. She was sent to the hospital at noon and the following formula was slowly injected into the rectum:

Sodium chloride	14 grams
Sodium carbonate (crystallized) . .	15 grams
Water	1000 c.c.

At 3.00 P.M. the uterine pain, the headache, and the nausea had disappeared and the patient went to sleep. At 4.00 P.M. the rectal infusion was given a second time and almost a liter was absorbed. At 11.00 P.M., 258 c.c. of urine were voided and the patient passed a good night, sleeping soundly. The following morning 500 c.c. of urine, very high in albumin, casts, and blood were passed. At three o'clock of this day, she again developed severe headache, nausea, and vomiting, and was unable to retain the rectal infusions or anything by mouth. At 10.00 P.M. all the symptoms had so increased in severity, that 300 c.c. of the

above solution were given intravenously. In fifteen minutes the patient volunteered the information that her headache and nausea were gone. She was comfortable until the next afternoon when periodic uterine pains developed, and the headache and vomiting returned. The patient was taken to the operating room, and the cervix was dilated slowly by hand. Delivery of the living child was accomplished in an hour and a half. This was followed by another intravenous injection of 645 c.c. of a solution containing 7½ grams crystallized sodium carbonate and 14 grams sodium chloride to the liter. In the following twenty-four hours 2200 c.c. of urine were voided, and as the nausea, vomiting, etc., had disappeared it was an easy matter to maintain such a urinary output by giving water and alkalies by mouth. Albumin and casts disappeared from the urine on the fourth day and the patient had an uneventful convalescence.

CASE 7. — (*Dr. W. A. Clark*, San Leandro, California.) Mrs. C. H., aged 35, and pregnant for the second time, presented herself for examination in March, 1911. She had menstruated slightly, and for the last time, January 22. A year previously she had given birth to a healthy child at term, though in the later months of her pregnancy her limbs and face had swelled, she had much headache, and her eyes had troubled her. At the time of her first visit, and repeatedly afterward, physical examination and examination of the urine showed nothing abnormal. On August 11, she showed a well-marked generalized œdema, and complained of headache, extreme restlessness, sleeplessness, dimness of vision, and constant nausea. Her urinary secretion had fallen to 500 c.c. per twenty-four hours, was highly acid, and high in albumin and casts. She was immediately sent to the hospital and kept in bed on a diet rich in water, alkalies, vegetables, and milk. Epsom salts were administered by mouth, and 0.85 per cent sodium chloride solution was repeatedly injected slowly into the rectum. On this regime all of her symptoms and signs including the albumin and casts disappeared, and the urinary output rose so that 2200 to 2674 c.c. were voided every twenty-four hours. August 26 the patient felt so well that she insisted on getting out of bed and busied herself about her room. On the second day following this renewed activity, her headaches again showed themselves, and her nervousness and sleeplessness returned. On August 29 her nausea and vomiting became severe, and her vision very dim. The œdema of the legs and face returned, and her urinary output fell slightly, to 1984 c.c. When the heat test was applied to the urine, the whole became solid. This condition continued until 11.30 P.M. of August 30, when the headache, nausea, vomiting, etc., were so severe that it was decided to give alkali and salt intravenously. The following formula was given:

Sodium carbonate (crystallized) . .	10 grams
Sodium chloride	14 grams
Water	1000 c.c.

In an hour the patient volunteered the information that her headache and nausea were better, and that she felt brighter. She slept well, and passed the next morning comfortably. Examination of the urine passed in the night and early morning showed a decided drop in the amount of albumin excreted. Even though the subjective symptoms of the patient continued well, the albumin content of the urine again rose so that on the morning of September 1 this was sufficient to make the contents of the test tube again set in a solid mass when boiled. The amount of urine obtained continued good, being 1984 and 2048 c.c. respectively, for the last two twenty-four-hour periods. It was deemed best to empty the uterus, and at 10.00 A.M. of September 1, dilatation of the uterine os by means of rubber bags was begun. Rhythmic pains began two hours later and as these increased in number and severity, the patient's headache and nausea increased, and the urinary secretion fell. At 4.00 P.M. the patient vomited and developed a twitching of the face and arms. This continued at intervals until 11.00 P.M. when two liters of the alkali-salt mixture of the composition previously used in this case were injected intravenously. Shortly after this, the subjective symptoms of the patient became better, and she fell asleep, passing a fairly good night, and examination of the urine again showed a decided drop in the amount of albumin present. The general condition of the patient continued good, and on the evening of September 2, she was delivered under chloroform anæsthesia of a 1750-gram, living, female child (left shoulder presentation with version). On the operating table the patient received 1000 c.c. of 0.85 per cent sodium chloride solution under the skin, and for subsequent treatment the patient was given this same salt solution by rectum and alkaline water (a gram of sodium carbonate in a glass of water every hour) by mouth. The urinary secretion on this regime never fell below 2200 c.c. On September 4 the albumin in the urine had dwindled to a trace, and on the next day it had disappeared entirely. Examination of the urine twice daily from this time on invariably showed an alkaline reaction to litmus paper and no albumin. The general œdema disappeared on the third day after delivery. On September 17 the patient was fully convalescent.

CASE 8. — (*Dr. N. A. Hamilton*, Franklin, Ohio.) Mrs. C., 27 years old, and a primipara in the seventh month, showed nothing abnormal on examination, September 8. On September 20 some albumin was found in the urine, and on September 27 it was present in abundance. Her general condition was good.

At 10.00 P.M., October 2, she was seized with sudden nausea and vomiting which continued through the night. At 3.30 A.M., October 3, she had short lapses of consciousness. Headache was severe; there was some œdema of the face and legs; the pulse was 100 and hard. Veratrum was given by hypodermic injection. At 8.30 A.M. her pulse had fallen to 52; her temperature was normal. No urine had been passed through the night, but at this time she passed 30 c.c. The patient was dizzy, still vomiting, had pain in her neck, and her sight was blurred. She was now given 800 c.c. of a strong (hypertonic) sodium chloride solution (1.5 per cent) by rectum. This was all retained. At 11.30 A.M. 90 c.c. of dark-colored urine filled with casts and containing so much albumin that on boiling it fairly set was passed. Another 800 c.c. of the sodium chloride solution were now given and at 2.00 P.M. an unknown amount of urine was lost with a stool. Twenty minutes later a convulsion lasting a minute occurred, and this was repeated a half hour later. The patient was vomiting, and could not distinguish colors. There was a general twitching of the muscles. A general anæsthetic was given at 3.30 and an attempt made to dilate the very rigid uterine os instrumentally. At 5.00 P.M. the membranes ruptured, and at the same time 30 c.c. of dark brown urine were obtained by catheter. At 6.00 P.M. the temperature of the patient was 100.2° F. by axilla. Another injection of 800 c.c. of the strong saline solution was given by rectum at this time and repeated at 8.00 P.M. but neither was retained well. At 10.00 P.M. a little urine (estimated as 30 c.c.) was passed with a stool. At midnight the patient's temperature was 100.2° F., she was dizzy, could not distinguish between men and women, and was unable to differentiate white from black. At this time she was given the following formula intravenously:

Sodium carbonate (crystallized) . .	20 grams
Sodium chloride	28 grams
Water	2000 c.c.

The injection required an hour. While giving the injection the patient volunteered the information that her nausea had left her, and that her headache was disappearing. At 2.30 A.M., October 4, she passed 75 c.c. of dark brown urine filled with casts and fairly solid with albumin on boiling. At 4.00 A.M. she passed another 75 c.c. and at 6.45 A.M. 95 c.c. During these hours she slept at intervals. When she awakened her headache and nausea were gone, and she could distinguish between gross objects, and recognize colors. From now on and through the day she was plied with water by mouth and five injections of 400 c.c. each of the above sodium carbonate-sodium chloride mixture were given by rectum. These were well retained. Urine was voided about every three hours, and in increasing quantity. By midnight, that is to say in the first twenty-four hours after the intravenous injection, she had voided 572 c.c. not counting two "large" voidings that were lost. The later portions of this urine were clearer in color and contained much less albumin than the specimens already described.

In the night of October 5, the patient went into labor, and at 8.00 A.M. forceps were introduced and she was delivered of a macerated fœtus. In spite of the exertions of labor she passed 320 c.c. urine, between midnight and the time of the delivery of the placenta. Through the night the alkali-salt enemas could not be retained, but through the day she took and retained four enemas of 400 c.c. each. In this second period of twenty-four hours she passed 734 c.c. of urine. After delivery, her temperature, which on the night before had risen to 103.6° F. (by mouth), fell to normal.

In the twenty-four hours of October 6, she received and retained four enemas of 500 c.c. each of the alkali-salt mixture, and drank freely of water (a glass every hour). She passed in this period 1840 c.c. of urine, not counting two voidings that were lost with the stools. The later portions of this urine contained only a little albumin. The patient was sleeping well, and relishing her toast, gruel, eggs, milk, and broth.

In the next two days the alkali-salt enemas were reduced to two daily, one night and morning, and then stopped entirely. She was given a liberal diet, and water was insistently given by mouth. Lemonade and orangeade were urged. When the alkali was no longer given by rectum, sodium carbonate (0.5 gram) was given in a glass of water as often as the patient would take it both day and night, and she was asked to salt her food liberally. Her urinary output on this regime was as follows:

October 7	3616 c.c.
October 8	3264 c.c.
October 9	3520 c.c.
October 10	2528 c.c.
October 11	2108 c.c.
October 12	2396+ c.c.
October 13	2432+ c.c.
October 14	2400+ c.c.
October 15	4096+ c.c.
October 16	3808 c.c.
October 17	3200 c.c.
October 18	1920 c.c.
October 19	1915 c.c.

The great rise in urinary output on October 15 followed an increase in the amount of alkali and salt given by mouth; the fall on October 18 a reduction of this.

The œdema had disappeared and the albumin dwindled to a trace by October 7. This trace persisted up to October 19. The patient developed a slight temperature (100.8° F.) on the fourth day after delivery, but following intrauterine douches with bichloride of mercury and iodine this fell so that only a temperature of 99.0° or 99.2° was registered in the afternoons up to October 17. From October 16 she was given an unrestricted diet, and on October 17 she sat up for the first time. On October 24 she "is downstairs, voiding an abundance of urine and happy."

CASE 9. — (*Dr. E. A. Majors*, Oakland, California.) Mrs. A. B., pregnant for the second time and at term was found in labor and delivered of a healthy living child, in an entirely normal way at 1.00 A.M. No previous history was obtainable. Following labor she fell into a deep sleep and at 5.00 A.M. it was impossible to arouse her. As there was no evidence of urinary secretion, she was catheterized at 6.00 A.M. No urine was obtained. At 7.00 A.M. she had two severe convulsions. Following this she lay in a deep stupor with rapid breathing. At 10.00 she was again catheterized but no urine was obtained. She now received by slow injection into the rectum the following:

Sodium carbonate (crystallized) . .	15 grams
Sodium chloride	14 grams
Water	1000 c.c.

Sixty c.c. of urine were obtained an hour after the beginning of the injection, and half an hour later another 130 c.c. filled with albumin and casts were obtained. At the same time the patient began to clear mentally. Three hours after beginning the injection she would respond to questions. She was plied with water by mouth. Later in the afternoon 500 c.c. of the above formula were again given by rectum and this was repeated next day. In the first twenty-four hours 1525 c.c. of urine were obtained, and 2240 c.c. in the second. At the same time the albumin and casts diminished and on the third day the urine cleared entirely. Uneventful convalescence followed.[1]

CASE 10. — (*Dr. William E. Kiely*, Cincinnati.) Three weeks before entering the hospital S. C. W., 38 years old, and a moderate beer drinker, became short of breath, suffered from headaches, and noticed a swelling of his legs and abdomen. Physical examination showed no disease of the heart or lungs, but fluid in the pleural and peritoneal cavities, with a general œdema of the subcutaneous tissues. The urine was low in amount, of high specific gravity, and contained much albumin, some blood cells, and hyaline casts. On this a diagnosis of (*chronic*) *parenchymatous nephritis* was made. After twenty-five days of rest in bed, a milk diet, a daily hot bath, saline cathartics, and digitalis, no improvement in his general condition was noted. There was now added to his diet a liter of water daily containing 25 grams of sodium chloride. Improvement in his general signs and symptoms began immediately, the urinary output rose, the blood disappeared, and the casts and albumin progressively diminished in amount. After ten days of this treatment he had improved most markedly, and at the end of twenty-five days all signs of his œdema and the effusions into his serous cavities had disappeared. At his own request he got out of bed and began to work about the ward, and shortly thereafter left the hospital free of all signs and symptoms, except for the faintest trace of albumin in his urine. In this state he has continued up to the present time (that is, for two months since leaving the hospital).

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[1] The methods of treatment as applied in this volume to nephritis can naturally be used in a whole series of clinical conditions in which a generalized or localized œdema as an expression of a generalized or a localized abnormal production or accumulation of acid is responsible for the signs or symptoms observed. A detailed discussion of this problem is out of order here, but it may not be out of place to catalogue some of the conditions in which excellent results have been obtained. Administration of water, alkali, and salt by mouth, by rectum, or intravenously, works excellently in the brain œdemas following injury, arsenic injections, etc.; in glaucoma; in the œdemas of heart disease; in the labored breathing of arteriosclerosis; in the delirium, twitchings, and convulsions seen in the acute infectious diseases; in the marasmus of infants and children; in bronchial asthma. *C. C. Fihe* has obtained excellent results by using salt, alkali, and water in hay fever and mucous colitis. In the latter condition *W. S. Kuder* has also reported good results. *James J. Hogan* uses salt and alkali injections with excellent effect in the pernicious vomiting of pregnancy even when no signs of nephritis or a generalized œdema are present.

CASE 11. — (*Dr. Julius H. Eichberg*, Cincinnati.) A. B., a 40-year-old lawyer, entered the hospital in April, 1911, with a history of kidney disease of eight years' standing. At various times during these years he had had a diagnosis of *chronic parenchymatous nephritis* made upon him. He had no enlargement of the heart and no increased blood pressure. The original cause of the nephritis could not be made out. When first seen the patient was passing about 400 c.c. of urine per twenty-four hours, containing 4 grams of albumin per liter and filled with all varieties of casts. On a milk and vegetable diet, sweat baths, and saline cathartics his urinary secretion increased somewhat, but his general condition did not improve, the number of grams of albumin lost each twenty-four hours did not decrease, and his œdema, ascites, etc., increased. After two weeks in the hospital he had a well-marked œdema of his legs, back, chest-wall, scalp, and face. The fluid in his abdomen extended to the umbilicus when sitting up. While his general hospital regime and diet were kept as before, he now had added to his drinking water and consumed each twenty-four hours 7 grams of dried sodium carbonate. After ten days of the carbonate administration his œdema and ascites disappeared completely, his urine increased to approximately 800 c.c. per twenty-four hours, though the quantity of albumin lost per twenty-four hours did not change perceptibly.

The patient at this point refused to continue taking the carbonate. In five days his weight went up 2½ kilos. *Dr. Eichberg* persuaded the patient to resume the carbonate, and at the end of another seven days his original weight had again been attained, and the visible signs of œdema which had developed when the carbonate was discontinued had once more disappeared. The urinary output amounted at this time to 800 c.c. daily, and the albumin dropped to 2.5 grams per liter.

At this point the patient refused a second time to take the sodium carbonate, and again the swelling of his legs and back developed, while his weight rose as before, 2½ kilos in less than a week. Following this period he returned a third time to the carbonate, and in six days had again lost his 2½ kilos and the obvious signs of an œdema. This is his state at the present writing when for four months he has been passing 1280 c.c. or more of urine daily, containing some casts and 0.75 gram of albumin per liter. He has left the hospital in fair condition, has a good appetite, sleeps well, and has resumed the practice of his profession.

The following case will serve to illustrate how the opportunities of relieving the acute manifestations of nephritis are decreased pari passu with the decrease in the absolute amount of kidney substance present.

CASE 12. — (*Drs. Jo. Hamilton*, Fruitvale, and *W. S. Kuder*, Oakland, California.) A. D. P., a 16-year-old high-school boy, first showed albumin and casts in his urine three years ago. During the past year, no analysis of his urine had been made. The boy's general health had been good. On September 4 he had been very active, and that night he slept badly. At six in the morning of September 5, he was found unconscious and in a convulsion. The convulsions were general, very severe, and practically continuous. Between the more severe paroxysms there was a constant twitching of the body and extremities. No urine had been voided, and none was found in the bladder when brought into the hospital at 1.00 P.M. and catheterized. Two liters of the following formula were at once injected intravenously:

Sodium carbonate (crystallized) . . .	10 grams
Sodium chloride	14 grams
Water	1000 c.c.

At 2.30 P.M., 64 c.c. of highly albuminous urine containing large numbers of granular and hyaline casts were obtained by catheter. Half an hour later a good amount of urine was voided into the bed. The patient seemed decidedly more relaxed and the convulsions gave way to less severe twitchings in the legs, arms, and trunk. The pulse which previously could not be counted dropped to 110 and the panting respiration fell to 24. At 5.00 P.M. 256 c.c. of urine were obtained by catheter. At this time the patient was perspiring profusely. At 6.00 P.M. two convulsions of moderate severity occurred. Permission to give another intravenous injection was denied, and so 400 c.c. of the formula given above were injected into the rectum. No more convulsions occurred at this time and the twitching stopped entirely. At 8.40 P.M. 96 c.c. of urine were obtained. At 11.00 P.M. permission to give another two liters, intravenously, of the sodium carbonate-sodium chloride-water mixture was obtained, and this was done. By 1.00 A.M. 352 c.c. of urine were collected by catheter, and at 2.00 A.M. 192 c.c. At 3.00 A.M. the patient had a slight convulsion, and at 4.00 he had a severe one and died.

A hasty physical examination of this boy immediately after being brought into the hospital showed no signs of œdema anywhere, readily palpable arteries everywhere, and an enlargement of the area of heart dullness toward the left and downwards, with no heart murmurs. On these findings a diagnosis of chronic interstitial nephritis secondary to an arteriosclerosis was made, and an unfavorable prognosis was given. It was felt (on the theory that uræmia represents an œdema of the brain) that the convulsions could be ameliorated, and that the secretion of urine could again be started, but more than this could not be promised as the degree of kidney atrophy, upon which the question of the ultimate recovery of the patient depended, could only be guessed at.

An autopsy made a few hours after death confirmed the clinical diagnosis of generalized arteriosclerosis with hypertrophy of the heart. The kidneys together weighed 112 grams, the surfaces were rough; the capsule was intimately adherent to the kidney parenchyma. On section the kidneys were a mottled gray, and so hard that they could not be broken by pinching with the finger nails. The cortex was reduced to a mere line.

The results outlined in the cases that have been briefly abstracted here seem to indicate very clearly that we have, in the administration of alkalies, sodium chloride, and water, a means by which we can rapidly combat those kidney symptoms that we are particularly liable to encounter in eclampsia, the acute toxic nephritides, the acute suppressions of urine that follow anæsthetics, surgical operations of various sorts, including those on the kidney in which the blood supply to this organ has been temporarily occluded, alcoholic debauches, too enthusiastic use of the nitrites,[1] etc.

While for the most part the alkali-salt-water mixtures were in these cases given by slow injection into the rectum, there is no danger, if a case is deemed sufficiently acute, in giving the mixture intravenously. To do this the elaborate surgical procedures usually adopted to make an intravenous injection (excepting the asepsis) can be largely dispensed with. In the way of apparatus we need only to insert an ordinary hypodermic needle into the rubber tube coming from the irrigation vessel which is filled with the solution to be injected. The irrigation vessel is raised to a proper height and, after all air has been driven out of the outflow tube, the hypodermic needle may be inserted through the skin or, after a small cut has been made into this, directly into one of the numerous veins in the forearm or at the bend of the elbow. It is best to simply hold the needle in position, but if so desired it may be fastened down with an adhesive strap. *The solution must be injected slowly so as to allow ample time for mixing with the blood.*

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[1] I have several times seen alarming falls in the urinary output and once a complete suppression of urine with death of the patient eight days later after the administration of nitrites to reduce blood pressure in cases of arteriosclerosis in association with chronic interstitial nephritis. As I have pointed out, *mere* reduction of blood pressure (except in cases of hæmorrhage) is scarcely to be looked upon as a therapeutic gain. Suppression of urine is bound to follow the lack of blood supply to kidneys which are barely getting enough with a high blood pressure. There is no justification for giving nitrites in chronic interstitial nephritis, unless we can show that while reducing general blood pressure we are not at the same time reducing the blood supply to the kidney down to a dangerous point. If an arteriosclerosis is killing a kidney, we can hope to help the situation only by treating the arteriosclerosis.

In the preparation of the solutions for intravenous injection it must be remembered that a carbonate cannot be boiled without driving off its CO_2 *and so converting it into the more alkaline hydroxide. To get a sterile solution the sodium carbonate is dissolved in as little cold distilled and sterilized water as possible. The sodium chloride is then dissolved in an appropriate amount of distilled water and sterilized by heat. After this solution has cooled sufficiently the carbonate solution is added to it. When dried sodium carbonate is used instead of the crystallized only one-third as much is to be employed, for crystallized sodium carbonate is approximately two-thirds water of crystallization. 3.7 grams dried sodium carbonate is equal to 10 grams of the crystallized.*

Some surgeons have advised and operated on acutely nephritic kidneys and stripped the capsule. In at least some instances good has followed such a procedure, but this can be expected only if the deciding element between the recovery of the affected kidney and death is thought to be measurable in the increased circulation obtainable through the kidney by stripping the capsule. Even after the answer to this is given in the affirmative, then before operating, the effects of an anæsthetic and the shock of an operation must be considered, and not unless these are taken to be negligible should the operation be done, especially since it appears from the experiments and clinical reports detailed in these pages that all that can be gained through an operation can be gotten by the simpler means of injecting the proper alkali-salt-water solutions.

These alkali-salt-water injections must also prove of service in surgical operations on the kidney, in which it is at times deemed necessary to occlude temporarily the blood supply to the kidney. The consequences of such a procedure are those of the experiments already detailed in which the blood vessels to the kidney were clamped. It has been shown by *C. C. Guthrie*[1] that perfusion with a physiological salt solution or a *Ringer* solution of kidneys so treated affects them more deleteriously than if they are left alone. This is because such salt solutions are not sufficiently concentrated to prevent the swelling, etc., of the kidney cells. Most perfusion mixtures lack moreover the necessary *colloids* — the water in them is free, which is not the case in blood and lymph.[2]

It is self-evident that that which will relieve a nephritis when once established should, when properly used, *prevent* such a nephritis from developing, and so we must consider how useful in the prophylaxis of nephritis must be the giving of water, alkalies, and salts. Especially serviceable must these prove themselves when preparing for an operation, in a threatened nephritis during pregnancy, when we deal with the acute infectious diseases, etc. There exist as a matter of fact any number of clinical facts to prove this. The milk diet has, not without reason, enjoyed for decades the popularity that it has attained. By giving milk we give a patient a very useful balanced ration of fat, carbohydrate, and protein. But we do more than this — we give water and salts. The water helps to wash out poisons and the salts contained in the milk have a concentration which just suffices to do away with the effects of giving an equal amount of water pure.

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[1] *C C. Guthrie:* Arch. Int. Med. **5**, 232 (1910).

[2] See page 193.

Similar reasoning explains the beneficent effects of giving "physiological" salt solution in large amounts by rectum, intravenously or subcutaneously, in various acute infections. It is again the combined effects of much water to wash out poisons and enough salt to counteract that accidentally lost[1] by the same procedure that washes out the poison. When in spite of such procedures the signs of a nephritis develop we need to press alkalies (alkaline drinks) and to give *more* salt.

We will conclude this section by giving a concrete illustration of the fact that, by increasing the alkali-salt content of the body, the opportunities for the development of the signs of a nephritis are greatly reduced. For such a test the albuminuria that develops in athletes after hard work was used, and with the following results:

In Experiment 19 on page 45 we detailed the quantitative findings regarding the excretion of albumin during an ordinary match basket-ball game, as determined by collecting the urine over the period of an hour and a half, in which time the game was played. In the following two experiments the urine was similarly collected, every precaution being taken to have the conditions for collection, regarding time, etc., as nearly the same as in the control experiment. The athletes were under no restrictions regarding diet, the only difference being that in the two experiments now to be detailed, the players took in addition to their ordinary food the juice of six sweet oranges in the first, and twelve in the second. The six oranges were consumed in the course of three hours preceding the game; the twelve in the twelve hours preceding the game. Oranges were chosen not alone because they are palatable, and so offer no difficulty in having the men take them, but because the salts contained in them have not only a decided capacity of combining with stronger acids, but the citrates, malates, etc., are the very salts which act most powerfully in reducing the solution of proteins in acids (as well as the swelling of organs under these circumstances, etc.). The game played in Experiment 37 was decidedly harder than that detailed for control purposes in Experiment 19, that of Experiment 38 fully as hard. The first five players were the same in all these three games, though the order in which they are numbered is not the same.

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[1] We have become all too inclined to consider *everything* that comes out in the urine as something that the intelligence of the kidney has found harmful to the body. It is scarcely as wise as this. It is rather hard to see, for example, why in a salt-starved animal that is being given water, the animal continues to eliminate some salt in the urine up to the moment of death, when *it is this very elimination that is killing the animal.*

EXPERIMENT 37. — Juice of six oranges fed the players. Urine collected for period of 1½ hours, during which time the play occurred. Phosphotungstic-hydrochloric acid-alcohol reagent used in the *Esbach* albuminometer.

BEFORE THE GAME.

Player.	Urine, in cubic centimeters.	Nitric acid test.	Heat test.
1	232	Negative	Negative
2	72		
3	30		
4	85		
5	280		

AFTER THE GAME.

Player.	Urine, in cubic centimeters.	HNO$_3$ test.	Heat test.	Esbach reading.	Albumin excreted, in grams.
1	62	Positive	Positive	1.25	.078
2	17			1.5	.025
3	152			0.75	.114
4	42			0.75	.132
5	228			less than 0.2	.046
					Av. .079

EXPERIMENT 38. — Juice of twelve oranges fed each of the players. Urine collected for period of 1½ hours, during which time the play occurred. Phosphotungstic-hydrochloric acid-alcohol reagent used in *Esbach* albuminometer.

BEFORE THE GAME.

Player.	Urine, in cubic centimeters.	Nitric acid test.	Heat test.
1	73	Negative	Negative
2	170		
3	187		
4	6		
5	23		
6	62		

After the Game.

Player.	Urine, in cubic centimeters.	HNO_3 test.	Heat test.	Esbach reading.	Total albumin excreted, in grams.
1	97	Positive	Positive	0.75	.073
2	56			1.25	.070
3	11			1.6	.018
4	44			1.3	.057
					Av. .054
5	44	Positive	Positive	0.6	.028
6	45			0.25	.011

Player number 5 played first half only; number 6, second half only.

Even when we count out the player in the control game who started with an albuminuria, and those in the succeeding games who did not play through, we still find that *the albumin secretion, both so far as average concentration and average absolute amount is concerned, is decidedly lower after feeding citrus fruit than without such feeding.*

4. On the Treatment of Œdema.

A generalized œdema constitutes so prominent a feature of certain cases of nephritis that it of itself becomes at times an object of treatment. Of the various methods that have been suggested for the control of this condition we will take up only one for discussion here, that of *the question of salt restriction.*

When we discussed in the earlier sections of this paper the enlargement of the kidney in the parenchymatous types of nephritis, we noted that this enlargement of the organ, which is in essence an œdema, can be reduced through the presence of salts, and as, for reasons already set forth, such œdematous swelling (just what occurs in the acute forms of nephritis) is a serious menace to the kidney, because it tends to shut off its blood supply, it was recommended to combat this condition by increasing the salt concentration in the nephritic individual. The thought, of course, at once suggests itself that this scheme of treatment might be extended to the treatment of the general œdema occurring in nephritis.[1] While such a course has for decades been approved of empirically, as evidenced by the use of saline purgatives, saline diuretics, etc., in the treatment of œdema, a marked reaction against the giving of salts in œdematous states has more recently set in. Of the scores of salts that might have been attacked in this way, sodium chloride has been especially marked out, and to-day it is a widely accepted belief that the presence of this particular salt in the body is responsible for the retention of water and so the œdema of nephritis, of certain cases of heart disease, etc. Evidence for the support of such a view has been entirely clinical. It has been noted that nephritic individuals with œdema and on a constant diet increase in weight when sodium chloride is added to their food, lose again when this is taken away, etc. From our knowledge of the general physicochemical activities of the salts it is absolutely impossible to understand why, first of all, sodium chloride should, of all the common salts that are found in the living organism, act in this specific way, and second, how it accomplishes the results that are claimed for it.

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[1] *F. G. Goodridge* and *William J. Gies* [Proc. Soc. Exp. Biol. and Med. **8,** 106 (1911)], while apparently accepting the teaching that the colloids of the tissues are responsible for the amount of water held by them, have taken exception to my assertion that an abnormal production or accumulation of acid in the tissues of the body plays an important if not the chief rôle in the production of œdema, in that these increase the power of certain of the tissue colloids to absorb water. While it would not at all surprise me to have it shown that some other or some series of other changes in the body tissues than an abnormal production or accumulation of acid is responsible for the increased hydration of the colloids here, which is the characteristic feature of œdema, the experiments of *Goodridge* and *Gies* do not do this. These authors base their criticism on the fact that fibrin threads suspended in such colloidal solutions as gelatine, peptone solution, egg white, blood, milk, and meat juice, do not swell visibly on the addition of acid to these solutions until this is added up to the point where it is "free" in the solution. When these authors add acid to the colloidal solutions in which they immerse their fibrin threads they increase the hydration by this means, not of the fibrin threads, *but of the colloidal solution* (they give this the "œdema"), as they would find if they measured its viscosity. Up to a certain point (maximum hydration under the influence of the acid) the addition of the acid would therefore tend to *prevent* the fibrin from absorbing water. Only if acid got into it and free water were available could we expect the fibrin thread to swell.

The question has also been asked if the views expressed in this book and in my volume on "Œdema" are correct, why in the "acidosis" of diabetes we do not have symptoms of nephritis and œdema. In answering this several facts must be remembered. First, the presence of some abnormal acid in the urine does not yet prove that the actual acidity of the body as a whole has risen. As a matter of fact *Yandell Henderson* and *Frank P. Underhill* [American Journal of Physiology, **28,** 275 (1911)] have recently shown that in the "acidosis" of diabetes just the reverse is probably the case, the body acidity is *diminished.* Secondly, in cases of diabetes in which the acid intoxication is great enough we do have casts and albumin in the urine. Furthermore, moderate degrees of œdema are difficult to discover by our ordinary rough clinical tests, and the high concentration of sugar present in the cells and fluids of the body also tends to reduce this œdema, for while the non-electrolytes do not reduce appreciably the swelling of certain hydrophilic colloids in low concentrations they do this in the higher concentrations.

In order to satisfy myself as to whether sodium chloride (or any of the other common salts found in our tissues) really has any such specific action in the production of œdema, I decided to test the matter out in a way that had not yet been done, and which was freer from objection than the experiments to determine this point that have been made on mammals. For experimental purposes I used frogs which had been rendered nephritic by being injected with uranium nitrate — a poison which is generally acknowledged as one of the best for the production of nephritis experimentally. By placing these animals in water they absorb all they need to saturate their œdematous tissues through the skin. Normal frogs (practically) do not change in weight when kept in water. Let it be added that these frogs were really nephritic — albumin and casts were plentiful in the urine, and the tables and photographs illustrate the œdema.

Parenthetically it is well to point out in this connection that we are in the habit of considering the generalized œdema noted in nephritis as secondary to the nephritis — in other words it is imagined that a condition capable of producing a nephritis first reduces the function of the kidneys, and because of this an œdema of the body tissues generally results. This is not correct. If the œdema were secondary to the loss of kidney function then we should be able to produce a generalized œdema experimentally most rapidly by complete removal of the kidneys. As a matter of fact, nephrectomized animals either develop no œdema at all or only a very slight one when compared with the œdema developed, say after the injection of uranium nitrate. This shows clearly that *the œdema of the tissues and the œdema of the kidney (nephritis) arise simultaneously, and from the same cause* — the uranium nitrate interferes with the oxidation chemistry in *all* the tissues of the body at once and leads to an abnormal accumulation of acid in them. In the kidney we call this condition nephritis; in the body tissues generally, œdema; in the eye, glaucoma.

As the following experiments show very clearly, *salts decrease the œdema of nephritis, and sodium chloride is no exception to this rule.*

EXPERIMENT 39. — Twelve frogs that have been kept in jars of tap water for several days have the urine squeezed from their bladders, are weighed, and divided into two sets of six each in such a way that the weight of any one frog in the first series is about that of a corresponding one in the second series. They are then all injected with 0.2 gram uranium nitrate into the dorsal lymph sac and placed in separate finger bowls each containing 100 c.c. distilled water in the first series and 100 c.c. *Ringer* solution in the second. The fluid in the bowls is changed once in 24 hours. The changes in the weights of the frogs are indicated in the following tables:

SERIES IN WATER.

Hours.	1		2		3		4		5		6		Average.
0.	33	%	35	%	40	%	42.5	%	49	%	60	%	0
18.30	44	(+33.3)	42.5	(+21.4)	51.5	(+28.7)	51	(+20.0)	53.5	(+ 9.1)	66	(+10.0)	20.4
40.15	48.5	(+43.9)	44	(+25.7)	56	(+40.0)	56	(+30.8)	57	(+16.3)	71	(+18.3)	29.1
64.15	48	(+43.0)	dead		56.5	(+41.2)	dead		62	(+26.5)	77.5	(+29)	34.9
88.30	dead		—		59	(+47.5)	—		69	(+40.8)	83	(+38.3)	42.2
					dead				dead				

SERIES IN RINGER SOLUTION.

Hours.	I.		II.		III.		IV.		V.		VI.		Average.
0.	33.5	%	39	%	42	%	42.5	%	52	%	65	%	0
18.30	38	(+13.4)	42.5	(+ 8.9)	44	(+ 4.6)	46	(+ 7.6)	54.5	(+ 4.8)	67	(+ 3.0)	7.0
40.15	41	(+22.4)	47	(+20.5)	49	(+16.6)	51	(+20.0)	59	(+13.4)	79	(+21.5)	19.0
64.15	44	(+31.3)	52	(+33.3)	55	(+30.9)	53	(+24.7)	64	(+23.0)	84	(+29.2)	28.7
88.30	47	(+40.3)	52	(+33.3)	57	(+35.0)	dead		65	(+25.0)	87	(+33.3)	33.6
	dead								dead				

Experiment 40. — Six frogs are weighed, each injected with 0.05 gram uranium nitrate into the dorsal lymph sac, and divided into two sets of three each. Those of the first are kept in separate finger bowls, each containing 100 c.c. water; those of the second in bowls containing 100 c.c. ⅙ molecular sodium chloride solution. The changes in weight observed are as follows:

Series in Water.

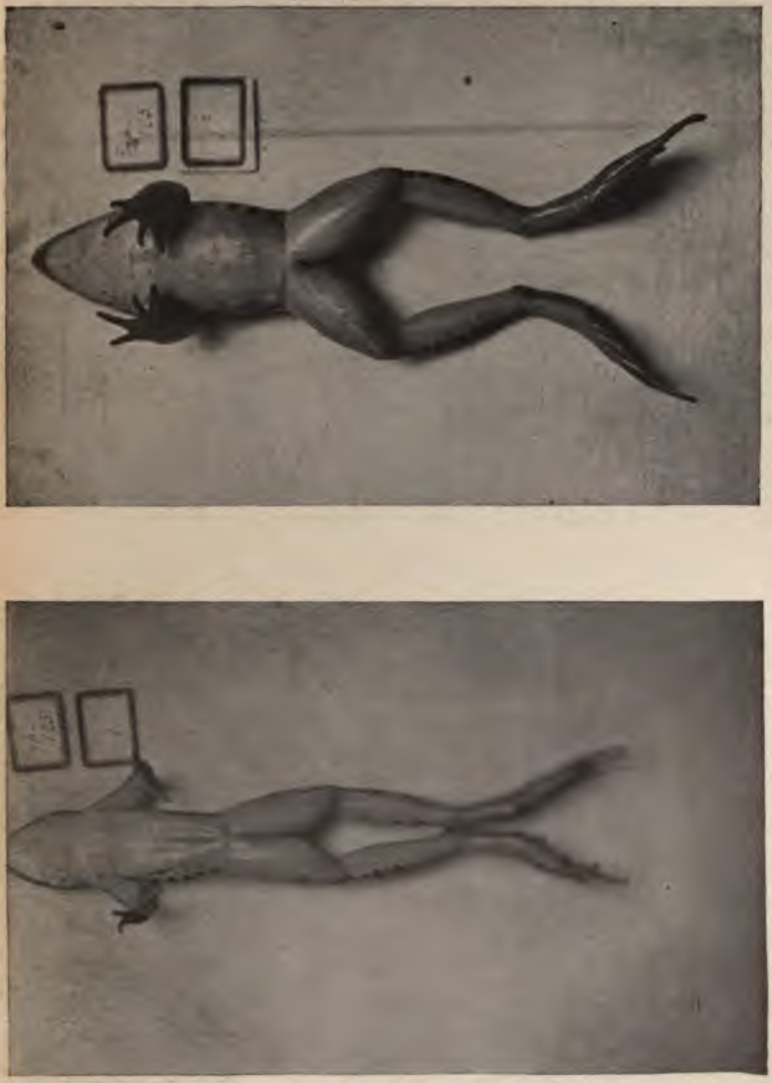
Hours.	1	2	3
0	30 %	27 %	24 %
18	33 (+10.0)	?	28 (+16.6)
26	36 (+20.0)	30.5 (+12.9)	29 (+20.8)
42	37 (+23.3)	35 (+29.6)	29.5 (+22.9)
68	38 (+26.6)	41 (+51.8)	?
92	39 (+30.0)	dead	30 (+25.0)

Series in ⅙ Molecular NaCl (0.975%).

Hours.	I.	II.	III.
0	34 %	29 %	26 %
18	32 (− 5.8)	29 (+ 0)	26 (+ 0)
26	33 (− 2.9)	30 (+ 3.4)	27 (+ 3.8)
42	33 (− 2.9)	31 (+ 6.8)	28 (+ 7.7)
68	38 (+11.7)	33 (+13.8)	30 (+15.3)
92	39 (+14.7)	35 (+20.7)	dead

The effect of the sodium chloride in reducing the œdema is evident to mere inspection. In Fig. 30, *a* and *b*, is shown frog 3 of Experiment 40, photographed at the time of injection and 42 hours later. Figure 31, *a* and *b*, shows frog III similarly photographed.

Are we now to conclude that the observations are wrong of those who have, by careful methods, noted an increase in weight (increase in œdema) after the feeding of salts, particularly sodium chloride, to patients afflicted with œdema? Not necessarily, though it must be said that grave objections may be raised against many of the clinical studies of this subject.



a

b

FIG. 30.

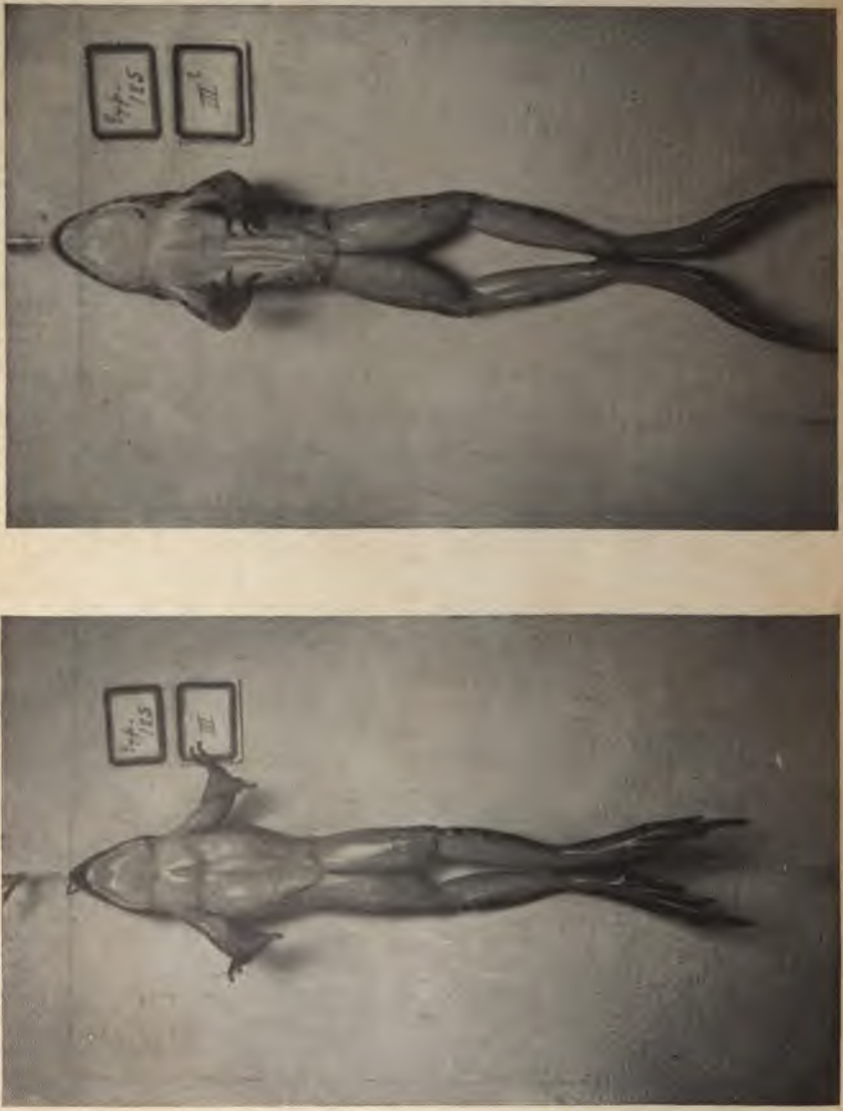


Fig.

b

When one studies carefully the cases in the literature in which salts have been found to increase œdema, one notes the fact that these are for the most part such as have been afflicted with ascites, hydrothorax, etc. When now any salt is given such an individual his tissues may very well give up water as do the frogs that have just been described. But where does the water go? The body weight as a whole can diminish only if this water is lost from the body through the urine (skin, gastro-intestinal tract, or lungs). But in nephritis the kidney does not so readily rid the body of water as in health, and so this water must go somewhere else. If it does not come out through some other emunctory (as in the diarrhœal stools at times observed in nephritis), *this water can only escape into the cavities.* What happens here is identical with the development of ascites, etc., in our experimental animals when we make these (especially after first rendering them œdematous by any means we choose) very rapidly give up their water by injecting a concentrated salt solution.

I saw a good clinical illustration of this in a patient of *W. S. Kuder.* A woman who for several weeks had been in bed, suffering from an extensive generalized œdema, with collections of fluid in the pleural cavities and abdomen, secondary to a heart muscle insufficiency of several years duration, had the abdominal effusion removed by paracentesis. In order to keep up the drainage some strands of silk were left in the opening made by the trocar. Seepage stopped at the end of twenty-four hours, but the silk was left in place. On the third day a liter of water containing 14 grams of sodium chloride and 10 grams of crystallized sodium carbonate, was given intravenously to combat the tissue œdema. This went down enormously, and as it disappeared the abdominal wound began to seep once more, so that pad after pad had to be applied to the abdomen to absorb the liquid.

It is clear therefore that while the œdema of the tissues is reduced, when salts or alkali are given an œdematous individual, the collection of fluid in the cavities is increased. When now we deal with a clinical case, the thirst[1] (from which the animals also suffer) leads the patient to drink water and so his total body weight (which in turn is taken as a measure of his œdema) increases.

But such a secretion of fluid into the peritoneal or other cavity would not by itself be a particularly serious thing, nor does this alone explain what happens in a persistent ascites. As we have long known, alike from experiment and from clinical observation, water and various salt solutions are readily absorbed from the peritoneal (and other serous) cavities. And yet the ascitic fluid is not absorbed. Why not? Evidently, after water or a salt solution has been secreted into the peritoneal or other cavity something must happen to this fluid which prevents its reabsorption. What this something is, is that *albumin is added to it.* Why this renders the ascitic fluid unabsorbable is apparent when the following considerations are borne in mind. With the origin of the albumin we are not immediately concerned, though it is of interest to recall, after what was said regarding the origin of albumin in the urine, that the ascitic fluid may be looked upon as an albumin-containing secretion from the peritoneal tissues which, in its general composition and mode of origin, finds an analogue in the highly albuminous urine secreted by the kidney in acute nephritis.

---

[1] Living animals and plants do not behave passively toward an abstraction of water. As soon as this occurs conditions develop in the cells which increase their avidity for water. Certain plants, for example, begin to develop acid as soon as we try to abstract water from them by any means. Animals behave similarly when they are robbed of their water.

As outlined in the discussion of our experiments on urinary secretion, special emphasis must be laid upon the fact that only "free" water is secreted by the kidney. The water of the blood is not "free" but is combined with the colloids of the blood. This water is not available for urine until it is freed from the colloids of the blood. The water of the blood becomes available for absorption (and subsequent secretion) by any tissue only as this tissue is first able to set the water free from the colloids of the blood and lymph or as the blood and lymph themselves suffer changes which make them yield up some of their water. Only such "free" water can be available for urine and conversely *it is only because the water in the blood is held in combination by the colloids here that not all the blood and lymph are absorbed from their respective vessels by the tissues.*[1] The colloids of the blood keep the water in the blood and prevent its total absorption by the tissues. When now we recall the fact that except for the presence of the red blood corpuscles, blood and lymph are practically identical in composition, and that *the so-called transudates in ascites, hydrothorax, etc., are identical with lymph, then we have no difficulty in understanding why these too may persist for days, weeks, or months in the body cavities without being absorbed. They are colloidal solutions in which the solvent is bound to the colloid, and not until the solvent is rendered "free" can it be absorbed.*[2]

---

[1] It is because no adequate (hydrophilic) *colloidal* solution has as yet been prepared that we are still far from possessing a perfusion liquid that will act better than our present "physiological" salt solutions in hæmorrhage, certain poisonings, and shock. *James J. Hogan* and I will shortly discuss the theoretical and experimental foundations for the preparation of such solutions in another place. See for a discussion of the factors involved in shock *Yandell Henderson's* excellent papers, especially Am. Jour. Physiol. **27**, 167 (1910).

[2] Certain experiments of *R. Heidenhain*, *E. W. Reid*, and *O. Cohnheim* might lead one to think that animals do absorb their own blood and lymph

In order to show that such colloidal solutions can, as a matter of fact, not be absorbed we need but recall how blood extravasations and lymph introduced into the peritoneal cavity, even in entirely healthy animals, may remain here unchanged and undiminished in amount for periods of time in which other aqueous solutions not containing such colloidal material (which in other words contain "free" water) are readily absorbed. The following experiments prove this very clearly.

EXPERIMENT 41. — A black and white rabbit is taken from his hutch, catheterized, and then weighed. His weight is found to be 1493 grams. A slight opening is made in the abdominal wall and traction made on this so as to make the entrance of fluid into the peritoneal cavity easy. A second rabbit has the carotid laid bare for as great a distance as possible in the neck. It is ligated high up, an artery forceps is attached to the coat of the vessel, a *Langenbeck* forceps is placed below this, and the carotid is severed. This second animal is now placed in such a position that the blood will flow directly from his carotid into the abdominal cavity of the first animal when the *Langenbeck* forceps is removed. The blood passes in a stream directly from the cut artery of the second animal into the peritoneal cavity of the first. This procedure is carried out at 2.40 P.M. The abdominal wound is closed immediately and the animal is weighed a second time to see how much blood has flowed in. The second weighing registers 1504 grams, which means that 11 grams of blood have flowed in. At the end of an hour the animal is killed by a blow on the head and immediately autopsied. The blood is found uncoagulated in the folds of the intestine. It is carefully aspirated into a tared flask and weighed. 11 grams of blood are recovered.

EXPERIMENT 42. — In an entirely similar way a guinea pig, weighing 520 grams, has a small opening made in its abdomen, and the blood from the carotid of a rabbit is made to flow directly into it. An increase in the weight of the guinea pig of 2.3 grams is thereby brought about. At the end of 1½ hours the pig is killed by

as such. This is not the case. For a discussion of this problem and a criticism of the experiments of *Heidenhain*, *Reid* and *Cohnheim* see my paper on absorption and secretion. Kolloidchemische Beihefte, **2**, 304 (1911).

a blow on the head and the unab for the ab-
tared flask. 2.1 grams are recovere in these

EXPERIMENT 43. — A black and ir ab-
grams, receives intraperitoneally in th m-
blood from the carotid of a second ra
former 26.0 grams. At the end of an
the unabsorbed blood is carefully recov
flask. 26.0 grams of blood are recovere

EXPERIMENT 44. — A white rabbit, w
intraperitoneally 45 grams of blood fron
hare. At the end of 70 minutes the anima
head and the blood found in the peritoneal ated into a
tared flask. 42.2 grams are recovered.

As the impression might be obtained that the failure of an animal to absorb its own blood is connected in some way with the nature of blood itself, and not merely with the fact that this is a solution in which all the water is held in combination with a colloid and, therefore, simply cannot be absorbed until first separated from the colloid, it was necessary to repeat this experiment with a colloidal solution other than blood. The result obtained with natural white-of-egg follows. In a similar way it can be shown that cubes of agar-agar do not lose in weight, and that gelatine solutions are absorbed only very slowly (not until the gelatine is " digested " and so loses its colloid character).

EXPERIMENT 45. — Into the peritoneal cavities of two guinea pigs, weighing respectively 537 and 563 grams, are injected by means of a large aspirating syringe respectively 20.8 c.c. and 31.2 c.c. white-of-egg (natural). At the end of an hour they are killed by a blow on the head and the unabsorbed peritoneal contents are aspirated into tared flasks. 18.4 c.c. are recovered from the first, 27.7 c.c. from the second.

In concluding this argument it is only necessary to show what is a familiar fact in physiology, that under identical conditions, water and salt solutions are readily absorbed (because they contain "free" water).

EXPERIMENT 46. — Three guinea pigs, weighing respectively 417, 397, and 419 grams, are each injected intraperitoneally with 20.8 c.c. respectively of water, 1/12 and 1/8 molecular NaCl solution. At the end of an hour the unabsorbed fluid is recovered and found to measure respectively 5.4, 11.8, and 13.0 c.c.

From what has been said it must be clear that little justification exists for the exclusion of sodium chloride, as for the exclusion of any other of the ordinary salts found in the body tissues, from the diet with the thought of thereby relieving the œdema of nephritis. Such a procedure does just the reverse. We have seen how the only untoward action of giving salts might reside in an increase of ascites, hydrothorax, etc. When such accumulations of fluid in the cavities become sufficiently great to demand attention on their own account, then we have to bear in mind that their composition is of such a character as to render their absorption without antecedent change (digestion of the protein colloids, reduction of their affinity for water) impossible. *Clearly, the thing to do then is to tap.*

Nor is there anything strange in the fact that the removal of a comparatively small amount, say of an ascitic accumulation, may be followed by a rapid absorption of the rest. As the amount of fluid in a serous cavity increases, the circulation through the surrounding tissues becomes more and more embarrassed, and so the possibilities for absorption progressively poorer. To relieve this pressure even somewhat will improve the circulation, not alone as to quantity but as to quality of blood passing through the part (a blood more nearly arterial in character replacing one highly venous in character), and so by favoring the removal of CO_2 and other acids always found in such serous accumulations[1] decrease the power of the colloids here for holding water, and so bring about further opportunity for the abstraction of water from the transudates found in these cavities. What holds for the "transudates" and their absorption holds also, of course, for the absorption of inflammatory "exudates."

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[1] *G. Strassburg:* Pflüger's Arch., **6,** 65 (1872); *A. Ewald:* Arch. f. (Anat. u.) Physiol., 1873, 663; *Felix Hoppe-Seyler:* Physiologische Chemie, **1,** 601. Berlin, 1877.

From what has been written in this volume, it is clear that we have held the evidence to indicate that nephritis results from any condition or combination of conditions which lead to the abnormal production or accumulation of acid in the kidney, and the action of this acid upon a series of such colloidal structures as characterize those found in the kidney. From these considerations we have then tried to obtain an "explanation" of the various phenomena which serve to characterize nephritis from a physiological and a morphological standpoint. The question now arises whether the acid factor is the only one concerned in producing the picture. This does not, of course, follow. Any condition present in the kidney and capable of exerting an action like that of an acid could add itself to the acid factor. What all such are or may be it would be purposeless to count up, — they are the factors which we know now, or may discover, to be effective in influencing the physical state of the body colloids, — but as a striking illustration we might mention the ferments. Not only do the proteolytic ferments, for example, bring about a splitting of the protein molecule which is similar or identical with the splitting produced by acids, but certain antecedent physical changes produced in the colloids by the action of the two are also identical, a point which *Wolfgang Pauli*[1] has recently emphasized from a physicochemical point of view in a way that gives it a special interest biologically.

[1] *Wolfgang Pauli:* Pflüger's Archiv, **136**, 495 (1910).

With this we will end for the present our discussion of nephritis, and our attempt to find a unifying interpretation for the myriad facts bearing upon its nature and cause, that fourscore years and a thousand workers have left us as a lavish heritage.

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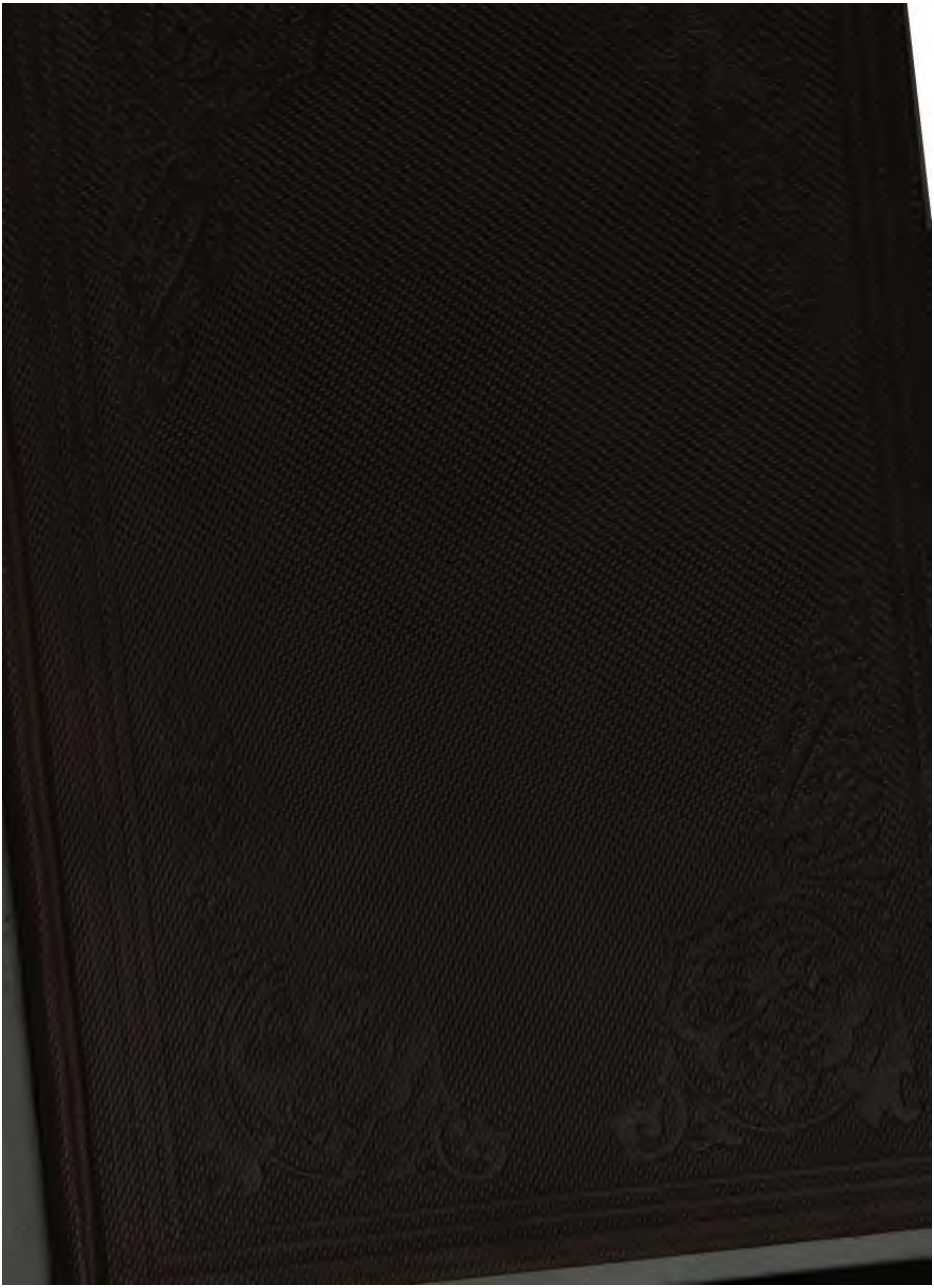

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ELEMEN

The Trustees of the Fiske Fund, at the annual meeting of the Rhode Isl
Medical Society, held in Newport, July 11, 1860, announced that the premiu
one hundred dollars offered by them on the following subject: "The morbid eff
of retention in the blood of the elements of the urinary secretion," had b
awarded to the author of the dissertation bearing the motto—

"*Prius cognoscere, dein sanare.*"

And upon breaking the seal of the accompanying packet, they learned that
successful competitor was Wm. W. Morland, M.D., of Boston, Mass.

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49 to 56 fluidounces. *Average specific gravity*, 1.020. *Mean amou* *solids*, 55 to 56 grammes (a gramme is 15.4440 grains, English).

Constituents.

Water	1345 to 1534 grammes.	
Urea	30 to 40 "	463 to 617 grs.
Uric Acid	0.5 "	or 7.5 "
Creatine	0.3 "	or 4.5 "
Creatinine	0.45 "	or 7.0 "
Sarkine Uræmatine Uroxanthine	undetermined.	
Hippuric Acid	0.5 "	or 7.5 "
Chlorine	6 to 8 "	92 to 123 "
(or Chloride of Sodium	10 to 13 "	154 to 200 ")
Sulphuric Acid	1.5 to 2.5 "	23 to 38 "
Phosphoric Acid	3.66 "	56 "
Potash and Soda Lime and Magnesia	undetermined.	
Earthy Phosphates	1.28 grammes,	19 "
Iron	undetermined.	
Ammonia	0.7 grammes,	10 "
Trimethylamine Carbonic Acid Phenylic Acid Damaluric Acid	undetermined.	

"The minor estimates account for 48 out of 55 grammes of solids, the estimates for 62 out of 66 grammes of solids."—Thudichum, *op. cit.*

From an examination of the above table, in connection with th sitions of the subject, it will be evident that we have only to indi pathological effects arising from the undue retention in the blood following constituents of the urinary secretion: Water; Urea; Uri Creatine; Creatinine; Hippuric Acid; Chlorine; Chloride of S Sulphuric Acid; Phosphoric Acid; Earthy Phosphates, and An The other ingredients of the urine, mentioned as being found in " mined" proportions, cannot enter into the list, in a practical con of the subject.

Water.—Taking up the urinary constituents in succession, w amine the results to be observed when that amount of *water* wh be excreted through the agency of the kidneys, is not so evacua portion of our subject may be comprehensively disposed of.

A very variable amount of fluid is evacuated from the bladde ent seasons of the year, and under peculiar and differing circ Thus, in cold weather, the amount of urine is greater, because *neous transpiration* is less. Again, when large amounts of cit., *et alii.*)

We may now dismiss the watery element from our subj at once to the consideration of the undue retention of the s of the urine in the blood.

UREA.—(Symbol: $\overset{+}{U}$.—Formula: $C_2H_4N_2O_2$.)[1]

This substance, "the principal product of the metamorph of nitrogenized food," and always a constituent of healt sidered a blood-poison when retained in the circulation. believe its action to be direct, others that it is indirect—or the agency of a product of its decomposition. It forms the m portion of the solids of the urinary secretion, and is purely matter, the elimination of which by the kidneys is absolut health and life. It is true that, in certain exceptional insta tities of it have been ascertained to be present in the blood, without compromising life, or even exciting those cerebral ally observed under such conditions; but it is to be presu the persons were, to a great extent, insusceptible of the ac else that the peculiar fermentation supposed to give rise to ing, by producing a noxious substance from the urea, did It is certainly very possible that some persons may be le the presence of urea in the blood than others; but, we re must be entirely exceptional. With regard to the consta sition of urea when retained in the blood, and the conseq another and a toxic substance, we have, as yet, too few fa to determine. If ever proved to be the rule, however, th certain unknown agencies might, in isolated instances, pr tion; and thus account for an apparent, or at least a temp from morbid consequences.

After extirpation of the kidneys in animals, and in Bri some other affections, urea is found pervading many of t body—as, the dropsical effusion, the blood, the perspirato vitreous and aqueous humours, and the liquor amnii.[2] Dr.

---

[1] Bird, Thudichum, *et al.*

Chemical Composition of Urea.

	THUDICHUM.	G. BIR
2C	20.000	C_2,N_2,H_4,O_2
4H	6.666	
2N	46.667	
2O	26.667	
	100.000	

[2] The presence of urea in the fluids of the body was first *Christison* in the Edinburgh Medical and Surgical Journal, Octo

kidneys do not, of course, affect animals *without* kidneys, an the analogy is not perfect, and hardly as safe to reason fr proverbially insecure foundation derived from analogical r rally. Dr. Hammond does not find that urea or carbona injected into the bloodvessels of sound animals, causes deat suffered extirpation of the kidneys, such injection proves f not discover from his experiments that urea, introduced d circulation, becomes converted into carbonate of ammonia. ments, at all events, go to prove the deleterious agency of product of its decomposition, when not promptly excreted whether it be due, as in the case of the animals experiment of the kidneys, or, as in certain conditions in the human retention in the blood by diseased, perverted, or obstructed organs. While the question as to the exact material acting still in abeyance, the *facts* relative to urea retained in the ductive of various "morbid effects," are indisputable, and a now proceed to examine them.[2]

GENERAL PHENOMENA REFERABLE TO THE PRESENCE O BLOOD.—From the fact that Bright's disease is the affectio is most frequently retained in the blood, it will be all the not to refer any of its concomitant phases to the action although it is very plausible, and some of the best medical present day are beginning to teach, that many of the so-ca Bright's disease may legitimately be referred to the presence circulation. Thus, Dr. Watson remarks the extreme readi organs of the body to become inflamed during an attack of B Especially is this found to be true, as all observers will testi to the serous and mucous membranes. Dr. Watson himself to this fact, and cites Drs. Bright, Christison, and Grego effect. He mentions, also, that M. Solon does not, in his minuria, consider this tendency especially prominent in Fra

Bronchial, pleural, pericardial, peritoneal, gastric, and in mations are well-known and common *sequelæ* of Bright's dis as to frequency, very nearly in the order above named. plausible to suppose that the abnormal condition of the by the presence of urea, may be productive of many of t tions. Dr. Watson, while suggesting this, speaks particul of the stomach and bowels, which so often follows or i

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[1] North American Medico-Chirurgical Review, March

[2] See Appendix, note A.

If we were to investigate thoroughly the disturbed chemis tions of the blood which might properly be imputed to reter the solid constituents of the urine, the limits of an essay, s quirements of the question now proposed seem to demand, attained, and, by the addition of the practical details, la We have interpreted the terms of the subject as indicating exposition of the phenomena of disease believed to be legitir to the abnormal retention of the solid urinary constituen endeavouring to present these, most of the results of the di tions and composition of the blood will, in fact, be made in concluding these general remarks, it is well to say tha observers, some years since, have been inclined to ascribe n tions of disease of slight intensity, and previously obscure fectly understood, to the presence of abnormal quantities blood.[1]

I. Cerebro-Spinal Phenomena attributable to U in the Blood.—(A.) A drowsy condition is often the fir clared manifestation of toxæmia by the presence of urea or of its decomposition in the blood. There are sometimes pre toms of less clear significance, but not always. Some w class them among the recognized *prodromata.*[2] This dro narily deepens into stupor and true coma, if it be impossil blood of the offending element. The re-establishment of a tendency to recovery from renal disease, may effect so but, unfortunately, the tide too frequently sets in the Coma may prove the final phase of the affection, and companied by disordered motility; or it may be combine and life may be terminated even more rapidly than if th not existed.

(B.) Convulsions of an epileptic form may be the there being no sopor, and consciousness being intact. respect, fully as unpromising as either of the two just

Among the first symptoms of uræmia may be m directed to the spinal marrow; and hence the sensitive imp make themselves morbidly apparent, as dizziness, headacl quently convulsive movements. We are not to inquire in *operandi* or etiology of uræmia, or of the other diseased co vening in the human subject, upon retention of the elements secretion in the blood; but—as we understand the questioı "morbid effects" only; consequently, we shall not occupy t by setting forth the received views and theories as to the dir modes of transmission of the deleterious influences, but will state succinctly the disordered vital phenomena observed, an gical appearances, if any, which are noted *post mortem.*

---

[1] Urea is always present in healthy blood, but in very s sometimes even not be readily recognized. Morbid effe upon its presence in large quantities, and upon its *accumu* abnormal increase, therefore, even if small, will exert an chemical and physiological information on this point, see dichum, and Carpenter.

[2] These will be specified hereafter; they are of a chara tion than the others; we will only mention—confusion unusual sluggishness, general *malaise.*

Uræmic symptoms may, of course, arise in both sexes fron or from mechanical obstruction to the excretion of the urin nephrosis, retroversion of the uterus, urethral stricture, and ureters; which latter, if dependent on an unrelievable cause, m fatal. The occurrence of what has been termed "uræmic (been witnessed in non-pregnant females, and in males, and so sidered as invariably belonging to the parturient state when uı The portion of Dr. Braun's work already cited, is devoted to of his belief that the convulsions observed during pregnar exclusively dependent on urinæmia.

After the appearance of the premonitory and of the earlie uræmia, the progress of the mischief will, of course, be vari patients, and also according to the amount and *cause* of urea. Thus, it would seem natural that a large amount of what *suddenly* thrown into the circulation, and kept there ance of the cause, should prove rapidly disastrous, and with marked and violent phenomena. When gradually intr

---

patient's not having come under notice until cerebral symptoms consciousness was so far lost that no commemorative history co in which no œdema of the ankles was perceptible—this peculiaı stertor has at once awakened my suspicions; has led to an urine and the breath, and to the discovery in the former of al casts, and in the latter of an undue quantity of ammonia.") (*C* latter fact is significant, in view of the doctrine of Frerichs a proves poisonous in uræmia; and the experiments and observa go far to confirm the opinion.

Dr. Reynolds adds: "The peculiar muscular condition cau disposed to consider as the result of spasm rather than paraly contraction may be either of sensori-motor, simply reflex, (only one of many phenomena which indicate excessive or those groups of motor action. This hypothesis is, of cou *the fact of* the difference is valuable."

prominent symptom.
together with a foot-note of much interest.

> "A few weeks ago, I saw an instance in which convuls
> birth were connected with the presence of albuminuria i
> nected, as it should be, perhaps, more correctly stated, with
> blood-poisoning or uræmia which is the result of albumi
> condition consists in a morbid accumulation of urea, or is
> supposes, by the presence of carbonate of ammonia in th
> decomposition of the urea, or is, as is more probable, the
> morbific agent in the circulating system, capable, like str
> the centric irritability or polarity of the spinal system t
> degree that, under this super-excitability, comparatively sli
> of irritation in the stomach, intestines, uterus, bladder, &
> convulsive attacks of a general form, like those of puerper
> *cit.*)

In the foot-note appended to the above passage, a
ticularly to the theory of Frerichs, Professor Simpson
important and interesting suggestions:—

> "If the blood-poison, which in albuminuria produces c
> be, as Frerichs believes, carbonate of ammonia, resulting fr
> urea, can we account for the power of chloroform in restr
> as it does, puerperal convulsions, upon the ground of its pr
> position? The inhalation of chloroform produces, as va
> shown, a temporary diabetes; sugar appears in the urine,
> also in the blood. The addition of a little sugar to urin
> vents, for a time, the common decomposition of its urea
> monia."

After mentioning the death of another child from co
on the third day after birth—the mother having had
and recovered—Dr. Simpson states that Dr. Weir, o
self found the urine of the child, like that of the mo
He also says he is unaware of any reported observ
of albuminuria and infantile convulsions; and ther
that the albuminuria may be common as a patholog
forms of the convulsions of infants—as in trismus
fantile diseases, he thinks, may be powerfully infl
as, for instance, sclerema, the "endurcissement o
laire" of French writers. Dr. Simpson had onl
Edinburgh, but was led, at the time of observing
suggest that the skin-bound disease itself, or at le
may be a variety or effect of Bright's disease in
into the cellular tissue, which constitutes the ma
being so far analogous to the anasarca occurring

In reference to the use of chloroform, and

(*Second Stag*
degree, partial or complete ;
muscles.

(*Third Stage*).—Appearance that of one suffering
vulsions.

Either of the last two stages may be present singly, the other r
ring ; or they may be combined and alternate.

2. *Disturbed Sensorial Manifestations. Early Stage.* ("Pre
of certain writers.)—Impaired vision ; transient, partial and
amaurosis (Reynolds, *op. cit.*) ; muscæ volitantes ; tinnitus a
porary deafness.

(*Later Stages*).—Deficient, and sometimes entire loss of
complete amaurosis ; permanent deafness—the latter less com
tion is seriously impaired, but not very frequently wholly
cognizance of impressions not taken ; but usual appreciat
the corporeal surface, felt. (Reynolds, *et al.*)

3. *Motorial Manifestations.* (*Early Stage.*)—More
clonic contractions of the muscles ; heavy and unwillin
stertor, "even when the patient is awake." (Reynolds.)

(*Later Stages*).—Voluntary movements mainly abs
be provoked by excitation ; continuance of clonic spe
vulsions, more or less strongly marked. Dr. Reynol
that the rigidity of the muscles observed during this
being sometimes excessive, "and much increased by m

4. *Mental Condition.* (*Early Stage*).—Listlessn
easiness ; confusion of ideas, impairment of memor
partial or complete, but light, delirium—noticed
"when falling asleep." (Reynolds, Braun, *et al.*)

(*Later Stages*).—The profound insensibility of
capable of dispersion—the patient can, by persis
soon, merging of this state into that of complet
Frerichs notices the fact that the usually mild
does not uniformly, attend this state, is characte
same word for a long time. A maniacal state
that disappears.[1]

The species of coma first referred to—wh
aroused—very much resembles that arising fr
poisons, acting with full force. Dr. Reynol
cit., p. 109), says he has noticed this sort
of urinæmic cases he has observed. He wri

---

[1] *See foot-note* 1, *page* 20.—"Some cases o
albuminuria, and where no eclamptic attacks
Simpson."—*Duncan* (*note to Braun*, p. 136).

organs may be particularly acted upon. Hemiplegia, hemerolopia, amaurosis, and impaired mental vigour may be mentioned. Œdema of the lungs and serous effusion into the cavities are noticed—the cerebral ventricles, even, being invaded by an urea-bearing serum. Life is too frequently destroyed, however, to enable observers to enumerate many cases and facts bearing upon this portion of our subject.[1]

II. Post-mortem Appearances.—It is universally conceded that very few structural changes, of consequence, and often *none whatever*, are found on necroscopic examination—after death from the mere action of uræmic poisoning—in the cerebro-spinal system. The apoplectic effusions and lacerations of the cerebral substance are only indirectly, if at all, referable to uræmia. The condition of this system is that which chiefly concerns us at this time; for we are seeking strictly for the effects, both vital and *post-mortem*, legitimately due to the toxic agent derived from the presence of urea in the blood. A full description, therefore, of what is found after death in the *kidneys*, does not seem to us pertinent to the question; for the usual and well-known renal lesions of Bright's disease are not the product, but simply the frequent cause, of the uræmic condition. We shall, therefore, endeavour to particularize the appearances presented after death by those organs which during life most strongly manifest the effects of the toxic agent, and with which it is most intimately brought into contact and relation—mentioning more succinctly such other concomitant lesions as have been observed. And in noticing the necroscopic phenomena in the cerebro-spinal system, we shall speak of such cases as have afforded the gravest indications of disturbance of the nervous centres during life, and especially decided coma and convulsions.

Brain.—Anæmic appearances, and a somewhat infiltrated condition, are noted; the consistence being most frequently diminished.[2] This state

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[1] The *mania* which sometimes follows the comatose state in uræmic eclampsia, is generally well recovered from; but should not be confounded with that symptomatic of puerperal pyæmia.—Braun; who refers to Helm, Litzmann, "and others."

[2] Romberg (*Nervous Diseases of Man*, London, 1858, Syd. Soc. Ed.) when mentioning the results of cadaveric inspections in cases of *eclampsia parturientium*—which affection, it should be borne in mind, is now referred by such high authority to uræmic intoxication—says—rather adversely to what we find recorded by others —that in the cranial cavity we generally find considerable congestion, increased density of the cerebral tissue, plastic and sanguineous extravasations between the membranes, and in the ventricles, in the latter chiefly when apoplectic symptoms, a profound sopor, stertorous breathing, &c., have been associated with the convulsive affection." (*Loc. cit.*) The points in which this account chiefly differs from that given by Dr. Braun, are the frequency of congestion, and the increase

Braun says, also, that inter-meningeal apoplexy is even more rarely observed than hyperæmia. He adds, that Helm and Kiwisch[1] very justly consider inter-meningeal apoplexy "as a secondary phenomenon produced by impeded circulation of the blood;" while it is looked upon by Litzmann as "a result of the uræmia."

Spinal Cord.—Examinations of the cord have been but infrequently made. (Romberg knew of *none* at the time of writing his *Treatise on Nervous Diseases*, the first edition of which was published in 1840 and the second in 1851.)

Braun states that Bluff, at one examination of the spinal cavity, "found much serum in it." Dr. Duncan reminds us, in this connection, that—as Dr. Christison first showed—the serum discovered in different regions of the body often has urea in it.

Dr. Todd, speaking of the condition of the cerebrum and spinal cord, after death following renal disease accompanied by coma and convulsions, says:—

> "The organic disturbance of the brain which accompanies and causes the comatose tendency, is, as I have already remarked, much less than the pulmonary affection. There we find nothing which the most zealous morbid anatomist could call inflammation; and, except the patient may have died in convulsions, we do not even find congestion—that most fertile of causes with a school of pathologists which is, I hope, fast disappearing. Indeed the brain is generally anæmic," &c. * * * (*Op. cit.*)

Dr. Simpson has reported (*Obstetric Works*, vol. i. p. 732) some cases of "puerperal convulsions connected with inflammation of the kidney," wherein effusion of blood and serum into the ventricles was discovered,

of the density of the cerebral substance, which the latter observer distinctly denies, as indeed do others. Romberg, whose whole description of the epileptiform convulsions of the parturient female is admirable, clear, and vivid, refers on the above points to Hauck (*Einiges aus dem Gebiete der praktischen Geburtshülfe;* in Casper's *Wochenschrift der gesammten Heilkunde*, 1833, vol. i. p. 133; and Velpeau, *Die Convulsionen der Schwangerschaft während und nach der Entbindung. Uebersetzt von Bluff:* Köla, 1835, p. 86). Romberg, as well as other authors, refers to the paucity of necroscopic facts connected with eclampsia puerperalis; and especially with regard to the spinal cord.* This is, even at the present day, true; but the latest observations, coming as they do from reliable sources, must be allowed the greatest weight. With regard to the appearances in the *brain*, then, a certain difference of statement exists between Romberg and other authors we have consulted. As to the *spinal cavity* and *the cord*, there are no new facts within our cognizance.

[1] Helm, Th., Med. Jahrbücher. Wein, 1839, bd. xx. s. 202; Kiwisch, Beiträge z. Geburtsk. Würzburg, 1846.—Braun, *op. cit.*, chap. VI.

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* Never had been examined when Romberg wrote; but has been since.

kidney (morbus Brightii), and purulent-like matter, with adherent lymph, or false membrane, in another. In a third case, purulent-looking matter could be pressed out from the renal papillæ; no effused fibrin or coagulable lymph was discovered. The microscope did not decide the "whitish turbid fluid" to be pus—only epithelial cells, in large quantity, were found. The last patient had repeated convulsions, and died comatose, but no mention is made of any cerebro-spinal lesions being observed. The effusion of blood, and the laceration of cerebral substance in the first case related by Dr. Simpson, were truly apoplectic, and not referable to the intrinsic action of urea contained in the blood; although doubtless the amount present therein must have been considerable, since Bright's disease existed.

Dr. Watson (*op. supra cit.*, vol. i. p. 493), speaking of the appearances observed after death from apoplectic coma, after having referred to such a result from the action of retained urea, uses the following language:—

> "On examining the brain, we may find a large quantity of extravasated *blood* spread over its surface, or lying within its broken substance; or a considerable effusion of *serous fluid* collected within its ventricles; or we may detect *no* deviation whatever from the healthy structure and natural appearance of the organ. The congestive pressure (if, indeed, it existed) has left no prints of its action."

The following observations, from the *Manual of Pathological Anatomy*, by Drs. Jones and Sieveking, are exceedingly apposite in this connection:—

> "The researches of Bright, Frerichs, and others have demonstrated the close relation of the state of the blood to cerebral disease; and science has shown, what, previously, was purely hypothetical, that the most fatal conditions may be thus induced without any palpable changes being wrought in the cerebral tissues. It does not, however, follow, that because we see no changes, none have taken place. The poison that we know to be in the blood may elude our chemical tests, and yet cause death. Then, seeing how limited our knowledge of the nervous system is, it is not to be wondered at that, although the manifestation of altered function is so great as to force the belief in its altered constitution, it is not in our power to prove the latter to the perception; but, as Dr. Watson remarks, 'whatever may be the nature of the unknown, and, perhaps, fugitive physical conditions of the nervous centres, thus capable of disturbing, or abolishing their functions, it is useful to keep in our minds a distinct and clear conception of the fact, that there must be some such physical conditions.'"

Mere uræmia, therefore—presuming the occurrence of convulsions and coma—it would appear, leaves the brain anæmic in appearance, and possibly somewhat softened (more dense, according to Romberg; refer to page 20); the more decided and destructive appearances are owing to rupture of vessels, and consequent extravasation, with its consequences, and to dilatation of the ventricles with serum.

and sometimes emphysematous. Dr. Braun, recording the fact that emphysema was long since observed by Böer, says that it is now considered "as always the secondary result of the fits"—*i. e.*, uræmic convulsions. *Op. cit.*, p. 62.

Heart.—This organ is reported to be usually "empty and flaccid." (*Braun.*) We may thence infer feebleness of circulation, and impairment of its own tonicity, and of that of the bloodvessels, by reason of the impoverished state of the blood, their natural stimulant.

Kidneys.—Generally, and according to some authors, always, the kidneys exhibit more or less extensive and advanced signs of Bright's disease. In cases where the retention of urea in the blood has been caused by some other agency—such as obstruction, etc., there would naturally be traces of congestion, and perhaps of inflammation, although not uniformly; a nearly natural state might well enough exist.

As we previously intimated, it does not seem necessary to give, in this place, an elaborate account of the changes wrought by granular and fatty degeneration of the kidney, in connection with uræmia; and for reasons already stated. Moreover, these general appearances are well known, and abundantly set forth in many treatises. Those who would see, however, an admirable and somewhat condensed account of the changes of this nature effected in the renal tissue in urinæmic cases connected with pregnancy (*eclampsia puerperalis, seu gravidarum*), should consult the chapter of Dr. Braun's work, to which we have so frequently referred. A few extracts only will be made by us, and those chiefly to call attention to certain prominent points in the renal necroscopic phenomena.

Dr. Braun bases his descriptions on the three forms of Bright's disease proposed by Frerichs.

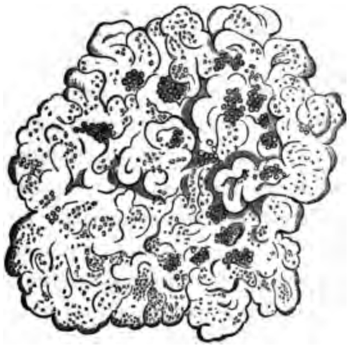
In the first stage, that of hyperæmia and commencing exudation, the surface of the kidney is smooth, the capsule is easily removed, the plexus of veins on the surface of the kidneys is dilated, and full of dark blood." (*Loc. cit.*, p. 62.)

"The pyramidal masses [renal papillæ] are likewise hyperæmic, and their injection is striped. The mucous membrane of the pelves and infundibula is swollen, and covered with vascular arborescence; and they contain a bloody fluid. Apart from hyperæmia, the finer structures of the kidneys do not appear to be essentially injured. Hemorrhagic effusions are very frequently observed, which sometimes take their rise from the glomeruli; sometimes from the vascular plexus of the tubuli uriniferi, sometimes from the veins on the surface of the cortical substance." (p. 63.) In the first stage, the epithelial lining of the uriniferous tubes is stated not to be essentially altered; the tubes themselves are often filled with exuded blood—"fibrin-cylinders."

In the second, or exudative stage, fatty degeneration commences and pro-are dark red. The infundibula have a dirty-red mucous surface. The glomeruli (vascular knots, Malpighian corpuscles), which may be drawn out with a curved pin, are covered with a fine granular matter, and partly with solitary or grouped fatty corpuscles, which, by the addition of acetic acid, become transparent.[1] Between the glomerulus and the capsule lies a thick stratum of firm exudation, of granular structure, and having fat droplets, and sometimes crystals of cholesterine.

The contents of the epithelial cells of the tubuli uriniferi next become degenerated—they are "decomposed in aggregations of granules."

Fig. 1.



Malpighian Corpuscle, from the kidney of a patient who died of *Eclampsia Parturientium.*—(From Wedl's Pathological Histology, p. 260.) "The surface is covered, partly with a fine granular substance, partly with solitary and aggregated fat-globules, which were not further changed by acetic acid or carbonate of soda. * *"—(*Loc. cit.*)

In the third stage, that of retrogradation, atrophy of the kidney is progressively induced. The pyramids of Malpighi and Ferrein are observed to be less atrophied than the cortical layer. At their bases, granulations occur between the straight tubuli, and press the latter apart.

The width of the renal pelves is increased, and their lining mucous membrane swollen and covered with a network of "varicose vessels, of an uniform grayish-blue colour."

"In those who die of uræmic eclampsia during pregnancy, atrophy of the kidneys is less frequently observed than the first two stages of Bright's disease." (*Op. cit.*, p. 69.)

III. URÆMIA IN CONNECTION WITH PREGNANCY AND PARTURITION.—If we receive the opinions of certain modern pathologists as true, the retention of urea in the blood of the pregnant female is productive, both to herself tical men in our profession; and, since the publication of his volume—and mainly, in Great Britain and this country, through Dr. Duncan's translation of the chapter on uræmic eclampsia—have elicited great attention, and will doubtless prove an incitement to yet more extended and close observation.

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[1] Wedl mentions that acetic acid rendered the fat-globules more distinct.

Whilst many have joined Dr. Braun in this new theory, there were at the time his work appeared, and probably still are, several distinguished names arrayed against it. These are all mentioned by the author himself, who also states the objections made by them, and gives what he considers the refutations thereof. Dr. Braun's belief, as declared in his treatise, is simply this: *that the convulsions caused by uræmic intoxication in acute Bright's disease, and puerperal eclampsia, are identical.* This proposition, as he tells us, has been energetically defended by Frerichs, Litzmann, Wieger, Oppolzer, himself, and many others; but it has been assailed by Marchal, Siebert, Depaul, Legroux, L'Huillier, Stoltz, Seyfert, Levy, in very valuable articles, and also by Scanzoni. With much anxiety these observers have tried to prove that the Brightian degenerations of the kidneys, which, it cannot be denied, are found in the bodies of those who have died of eclampsia, are consequences merely of the convulsions—only accidental, secondary phenomena of the hyperæmia caused by the eclampsia, and of hydræmia (*plethora serosa*).

Scanzoni, whose arguments against Dr. Braun's views are summed up and given by the latter author, refers the true *eclampsia parturientium* to an "irritability of the motor system of nerves which has been induced by pregnancy, and increased by the act of delivery."

The arguments *pro* and *con* have been actively carried on; and Scanzoni's conclusions were replied to by Wieger in June, 1854, and by Litzmann in 1855. In addition, the industry and zeal of Dr. Braun have enabled him to collect a truly imposing array of facts from *post-mortem* observations made by himself and other reliable practitioners, and in the majority of which abundant evidence of Brightian renal lesions existed. In some of the cases, where hyperæmia of the kidneys was found, microscopical examination was prevented by "accidental obstacles;" but the author does not consider this "any proof of the absence of Bright's renal exudation." Dr. Braun, while setting forth these investigations, says that Wedl[1] explains the non-discovery of fatty degeneration in the kidneys in several instances of death from eclampsia, "by the fact that in many cases a dissolution of the Malpighian bodies is effected by the fluid exudation, and hence in every diffuse inflammation of the kidneys an evident fat-metamorphosis of the contents of the Malpighian capsules does not ensue."[2]

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[1] Grundzüge der pathol. Histologie, Wien, 1854, S. 306.

[2] Loc. cit., pp. 74, 75.

Hasse, according to Dr. Braun, has never seen eclampsia puerperalis without Bright's disease. The necroscopic and microscopic observations of Wedl, Gustav Braun, Lumpe, Hecker, Devilliers, Regnauld, Simpson, Blot, Cahen, Wieger, Litzmann, Credè, Sabatier, and Hohl have contributed to establish the theory propounded in Dr. Braun's volume.

In reference to the *etiology* of "eclampsia parturientium" ("uræmic eclampsia" of Braun), Romberg[1] only hints at the agency which Braun has distinctly announced as, in his opinion, the chief efficient cause. Thus, while the latter ably demonstrates his views as to the retention of urea, and the accompanying albuminuria, the former refers to "retention of urine owing to pressure of the gravid uterus upon the bladder;" and afterwards adds: "Future investigations must determine whether albuminuria, which often supervenes during pregnancy, may, when fully developed during the last months, possess any etiological influence." The "investigations" of Braun and others certainly seem, if not already to have determined this point, likely to lead shortly to a satisfactory settlement of the whole question.

Supposing, then, in conformity with the new doctrines thus announced, that the convulsive attacks and intervening coma observed in puerperal patients are owing to toxæmia by retained urea, let us examine the collateral results of such a condition—first, in regard to the mother; and next, as respects the fœtus. Having already detailed the general effects produced upon the system by uræmic intoxication, we may properly direct our notice, at present, to the influence exerted upon the *puerperal state,* and upon the *life* of the mother and that of the fœtus.

Referring to our previous enumeration of the results, both vital and *post-mortem,* which are observed after genuine uræmic convulsions, we would only add thereto that the *uterus and its appendages* are generally found healthy after eclampsia puerperalis, or, at all events, do not necessarily deviate from their usual condition after labour has terminated; unless, of course, there has been some pre-existent or concomitant disease in, or alteration of, the organs. The infrequency of metritis and peritonitis is mentioned by some observers;[2] but Churchill[3] speaks of the great tendency to abdominal inflammation after the labour is over, and quotes Denman, who first mentioned this, and Collins and others, as confirming it. Braun also refers to the danger of puerperal affections coming on after eclampsia, especially if "an epidemic of zymotic diseases prevails."

The *spleen* is said to exhibit "the large dimensions it possesses in pregnancy and childbed."[4]

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[1] A Manual of the Nervous Diseases of Man; Sydenham Society's edition, London, 1853, vol. ii. p. 189.

[2] Romberg, Velpeau, *et al.*

[3] Theory and Practice of Midwifery.

[4] Braun, op. cit., p. 62.

by uræmic intoxication during the puerperal state.

1. *Influence of Uræmic Eclampsia on the Duration of Pregnancy.*—Uræmic eclampsia is generally sudden in its accession, prompt in its results; and the testimony of those who have had the most experience in regard to it, is that it either causes death rapidly, or else that it is completely and with considerable celerity recovered from. Long consequent illness and sequelæ, *from the eclamptic state merely*, are not common. The true uræmic eclampsia occurs in the majority of cases in the latter part of the period of pregnancy. It may, also, only appear at the time of the labour itself; after the child is born, and before the after-birth has been delivered; or, finally, during child-bed. When supervening within the latter half of utero-gestation, premature labour is the result—as a rule.[1]

The latter two months of pregnancy are stated to be peculiarly obnoxious to the occurrence of convulsions. (Churchill, Romberg.) The *cause* of premature labour is either excitation of uterine contractions by the power of the abnormal action going on in the nervous centres,[2] or it may be, partially at least, ascribed to the presence of a dead fœtus, whose destruction is referable to the eclamptic condition. Ramsbotham, we observe, does not think the latter occurrence a cause. Churchill queries whether it may not be such; and the supposition is at least plausible. Dr. Copland (*Dict. of Med.*) speaks of cases where "the child has been unexpectedly born during the violence of the convulsions, as if expelled by them with unwonted celerity." Again, he states that the worst forms of the attack are often attended by a firm, spasmodic constriction of the cervix uteri, preventing the expulsion of the fœtus.

2. *Influence of Uræmic Eclampsia upon the Life of the Mother.*—Although puerperal convulsions—we here use the term, let it be remembered, as synonymous with uræmic eclampsia—are comparatively a rare affection, yet they make up for the element of infrequency of occurrence, by violence of manifestation and an alarming ratio of fatality. As the liability to an attack is greater towards the last of the period of utero-gestation, so, generally speaking, is the danger to the life, both of mother and child, at that time. Not only is this true if we merely refer the eclamptic condition to the increased sources of irritability to which the nervous system has

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[1] It is well known that Bright's disease, without any other influence, will cause premature labour; Braun says this is true in about 25 per cent. of cases. Add *convulsions*, and the danger is manifestly increased.

[2] Blundell (Principles and Practice of Midwifery, Am. edit., p. 418), referring to this point, says: "Sooner or later, * * if the fit continue, parturition commences of itself, without the interference of the accoucheur; and * * a sudden emersion of the fœtus occurs." He also refers to the occurrence of delivery during convulsions, unknown to the attendants.

with increased morbid force—especially upon fœtal life. Again, the danger from convulsions diminishes according as they approximate to the term of delivery; and we are told, by a most competent authority, that the fits diminish in force in 31 *per cent.* of the cases, cease entirely in 37 *per cent.*, and only continue of the same intensity in 32 *per cent.*, *after the uterus is evacuated.* (Braun.)

Dr. Braun refers to 15 deaths out of 45 cases, of which he has published accounts—being exactly *one-third.* He speaks of nine cases occurring in his practice within the last three years, all of which terminated in recovery. Thirty *per cent.* of the cases, it is estimated, prove fatal. Romberg gives a higher ratio of mortality. His statement is, that above one-half of the women attacked, died within twelve, twenty-four, or thirty-six hours. Churchill finds from his statistical investigations, that the proportion of fatal cases is above one-fourth. He intimates that there has been a tendency, of late, to diminution in the mortality-rate, which, at one time, he asserts, was very much larger. It has not been thought that much, if any difference as to fatality can be ascribed to early or late supervention of the affection; at all events, lateness of attack has not been allowed more weight, in this respect, by observers, when it is a first case. Some patients have several attacks in successive pregnancies, and finally die in one. A reiteration, therefore, of the accident, must be deemed of unfavourable augury. The concomitance of coma, with apoplectic stertor, and the approximation of the fits, so that they become, as is sometimes the case, almost continuous—and especially when these conditions obtain in plethoric and strongly constituted patients—are, almost without exception, fatal elements.

Recovery from the mere eclampsia may take place; and there may be some extensive dropsical effusion, some injury to the brain or spinal cord, or a permanent and increasing œdema of the lungs, disease of the heart, etc., which will compromise life at a later period; but, as a rule, if the patient escape the eclampsia, and its *immediate* results, recovery is usually not tardy, and, moreover, is complete. The occurrence of rupture of the uterus, in itself sufficiently grave at any time, we need scarcely say, very greatly aggravates the unfavourable prognosis attaching to eclampsia. Dr. Copland remarks (*Dict. of Practical Medicine*), that puerperal convulsions "should never be considered devoid of danger, more especially when they occur after delivery, or in consequence of great exhaustion of vital power, or of uterine hemorrhage. When they are slight, are unattended by stertorous breathing, or by paralytic or apoplectic symptoms, and when parturition is so far advanced as to readily admit of its completion by art, less danger may be feared."

and Blundell speaks of *post-partum* convulsions as being the most dangerous.

3. *Influence of Eclampsia on the Life of the Fœtus.*—We have already intimated the danger arising from eclampsia parturientium to the life of the fœtus. Relatively, it is even greater than that threatening the mother. In referring to this point, those who have had the largest experience, use such expressions as the following: "In almost all cases the child is stillborn, often putrid." (Churchill, *op. cit.*) "The life of the fœtus is endangered so long as it is nourished by the uræmic blood of the mother." (Braun, *op. cit.*) "The infant almost invariably dies when the disease occurs during the last months of pregnancy; it may be saved when the eclampsia supervenes during parturition." (Romberg, *op. cit.*, p. 189.) "The infant is generally, though by no means universally, born dead, when the woman has been the subject of convulsive seizures, especially if the attack has occurred early in the labour, and continued for any length of time." (F. H. Ramsbotham, *Principles of Obstetric Medicine and Surgery.*) The latter author pointedly and happily refers to *toxæmic action* on the blood of the fœtus as the most likely cause of its death *in utero;* and mentions a case from Spence, where the child being removed alive by Cæsarean section from a mother just dead from convulsions, died itself, in convulsive paroxysms, in less than an hour. The latter statement leaves us to presume a poisoned condition of the blood. M. Ménard states, that, in the majority of cases of death by convulsions, previous to delivery, the child has been found dead; the contraction of the features and extremities showing that it had participated in the affection of the mother. Dr. Copland, who notes this remark (*Dict. of Med.*), says that it "wants confirmation."

We thus see that the likelihood of the life of the fœtus being maintained after eclampsia has been declared in the mother, is extremely small, as might, indeed, be expected; and if the child be born alive, there is great probability that it may either not survive long, or that it will be more or less morbidly affected by the accidents occurring during its intra-uterine existence.

Hereditary transmission of eclampsia, uræmia, or Bright's disease of the kidney, to a suckling, says Dr. Braun, "has not yet been demonstrated, and only Simpson has found albuminuria in a suckling born of an eclamptic mother." Dr. Duncan, in a foot-note to the paragraph from part of which the last remark is taken, says that "if the uræmia persists in a nursing woman, urea may be present in the milk, as has been shown by several observers, and may disturb the health of the suckling."

Synonymes.—Lithic acid; Urylic acid.—PROUT, BIRD, *et al.*

This substance is the next constituent of the urine, in the order of enumeration we follow; and the effects of its retention in the blood will therefore now engage our attention.

It is recognized as a constant ingredient of healthy urine, and holds a very intimate relation to urea. (Thudichum, *op. cit.*) "It forms less than $\frac{1}{2000}$ part of the urine in man; but its proportion varies much in different animals." (Dr. George Johnson, *op. cit.*, p. 50.) In the blood, it is always found in union with an alkaline base; and it is not soluble in that liquid. It appears in the blood in the form of urate of soda, or of urate of ammonia. (Liebig, Simon, Thudichum.) Dr. Thudichum states that the urates are always acid salts—*i. e.*, that there is excess of uric acid—and he has advanced some ingenious reasons for denying the accuracy of Dr. Golding Bird's theory and explanation of the secretion of uric acid in the form of urates. With this chemical discussion we have no concern; the indication of the pathological states induced by retention of the acid in the blood, in the form above specified, being now our object. Before approaching the subject in detail, however, it does not seem particularly out of place to allude to a practical remark by Dr. Thudichum (*op. cit.*, p. 100) upon the deposition of the urates from the urine. Researches and observations in reference to this point, cannot fail to be of importance in the treatment of such cases. Dr. Thudichum says :—

> "If the presence of a deposit of urates be taken as an indication of the saturation of urine by these salts, and if the latter be assumed ordinarily to be of the usual amount, deposits of that kind become more valuable as signs of a diminished secretion of water by the kidneys than of any other symptom. As the appearance of a deposit of urates is always accompanied by morbid sensations and objective symptoms—in the healthy by thirst at least, if by nothing more—the conclusion is simple enough. *The individual whose urine has deposited the urates does not drink water enough, and must drink more, and must drink so much that the urine, at the ordinary temperature of the air, shall remain clear.* Of course, in some cases this will be neither possible or advisable; but in most cases of acute and febrile disease it should be a plan of treatment. I have certainly seen it attended by beneficial results in many cases; I have also observed the contrary—want of water in the system—to be a source of disease."

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[1] Thudichum.

Chemical Composition of Uric Acid.

	THUDICHUM.	G. BIRD.
Carbon . . .	35.714	$C_{10},N_4,H_4,O_6,C_2,H_4,N_2,O_2+2C_4,NO_2=168$
Hydrogen . . .	1.191	
Nitrogen . . .	33.333	
Oxygen . . .	19.048	
Water. . . .	10.714	
	100.000	

GOUT.—Whenever, from failure to eliminate the uric acid from the blood, that substance accumulates therein, the abnormal effects of its presence do not long delay their manifestation.[1] It is well known that the ingestion of large quantities of highly-azotized food, and a rich diet generally, together with the free use of malt liquors and of acid wines—Madeira amongst others—is productive of an abnormal increase of uric acid in the system; and, consequently, luxurious livers have long constituted the majority of sufferers from gout—a malady which abundantly declares its *fons et origo*, by the tendency to abundant deposition of the *urate of soda* in different parts of the body; its seat of election being the smaller joints—as those of the toes and fingers. In the latter, the deposit is often very plentiful. We have seen not long since—and the occurrence may not be very uncommon—a patient who could write his name with his "chalk-stone" knuckles; a woful example, truly, of diverted and arrested excretion![2]

As has been previously mentioned, Dr. Garrod, of London, first called attention, not only to the presence of uric acid in healthy human blood, but also pointed out the fact of its abnormal amount in connection with gout. He did not, however, then wish to be distinctly understood as declaring the acid the sole *materies morbi* in that disease, as may be seen by his remarks in a "Postscript" to his highly interesting paper, communicated to the Medico-Chirurgical Society, upon the subject. This important contribution to scientific medicine was read before the Society,[3] February 8, 1848, and the postscript just alluded to bears date July 26, 1848. (Vide *Medico-Chirurgical Transactions*, vol. xxxi.)

Daily observation tends to show that the relation of cause and effect may more and more safely be predicated in regard to the presence of an excess of uric acid in the blood and the phenomena of gout. Writers upon the subject, both near the time of Dr. Garrod's first researches, and later, have varied somewhat as to the completeness with which they have expressed themselves in respect to establishing uric acid as the active agency in gout. The majority of testimony seems to be affirmative. Dr. Watson (*Principles and Practice of Medicine*, 1848) seems to have then regarded the morbid agent as recognized. We find, indeed, in the edition of Dr. Carpenter's *Physiology* published in 1846, very positive language as to the conspicuousness of uric acid in gouty affections; he says: "When it [uric acid] is imperfectly eliminated, we are assured of its accumulation in the circulating fluid, by its deposition, in combination with soda, in the neighbourhood of the joints—forming gouty concretions, or chalk-stones." He thus appeared to recognize the cause of the diseased condition as lithic acid. There are those, however, who, even at the present day, speak with less distinctness as to an excess of uric acid being the sole and sufficient *materies morbi*. Thus, Dr. Barclay (*A Manual of Medical Diagnosis*, London, 1857) writes: "The researches of recent times have gradually led to the discovery of an important element in gout—the presence of an excess of uric acid in the blood. This knowledge holds out a prospect of our arriving ultimately at more accurate diagnosis; at present, it is only in the hands of a few that such a chemical test can be relied on." The opinion is a very guarded one—decidedly non-committal; we think more influence than it implies may safely be allowed to the "element" in question.

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[1] Bernard recognizes the accumulation of uric acid in the blood, either by arrest of the renal function, causing its elimination to cease, or by an exaggerated production of it, as in gout. (*Liquides de l'Organisme.*)

[2] An instance of this is related by Dr. Watson (*op. cit.*), and Dr. Todd has alluded to the condition. After all, cases of this extreme nature may not be so common as we have intimated.

Dr. Garrod (*On the Treatment of Gout and Rheumatic Gout*) remarks upon this point: "Comparatively few gouty patients become the subjects of visible chalkstones, at least to any extent, or such as to induce deformity; at the same time, I am convinced that their occurrence in a slight degree is by no means so rare as has been generally assumed. Sir C. Scudamore stated, that in 500 cases of gout he only found them 45 times, or in less than 10 per cent. From my own experience, I consider these numbers far below the real proportion, being confident that their existence is frequently overlooked, as they are sometimes deposited in parts of the body scarcely to be expected." Dr. Garrod thinks that gouty concretions are more frequent upon the cartilages of the ear than anywhere else; contrary to what has usually been recorded. He refers to the *Medico-Chirurgical Transactions*, vol. xxxvii., 1845, pp. 74, 75.

[3] By Dr. C. J. B. Williams, upon some of whose patients Dr. Garrod's experiments were made.

It will, at least, not be disputed that gout is a blood-disease. Amongst many other observers who might be cited on this point, we select Dr. George Johnson, as furnishing comprehensive testimony. Referring to gout as a cause of renal disease, he says: "It would be useless to occupy the time of my readers by lengthened arguments to prove that gout is a blood-disease, since all the phenomena of the disease clearly indicate such an origin, and can be explained on no other supposition." (*Op. cit.*, p. 78.) He then alludes to the intimate connection between gout and the uric acid diathesis. Thus, then, when such a diathesis prevails, or when, by some obstructing agency, the elements of the urinary secretion are retained and accumulate in the blood, the gouty accidents, amongst others, prevail. If uric acid be prominent, the corresponding series of symptoms seems as sure to occur, as does that following the retention of urea when *that* substance is retained, in excess, in the circulation.[1] If the uric acid, therefore, is received as the true *materies morbi* in gout, we have, at once, the following easily-deduced sequence of morbid effects:—

First, deficient depuratory action; next, accumulation of uric acid in gout—amongst others, as Dr. Johnson points out, renal disease. Under the light of modern pathology, we do not think the above any too weighty a burden to lay to the charge of retention and accumulation of uric acid in the blood.

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[1] The blood contains, as Dr. Garrod remarks, "mere traces" of uric acid *in health.* This fact, however, in no degree invalidates the agency of the acid as *a causative element in gout.*

There may remain a certain quantity of uric acid in the urine, at the same time that the analysis of the blood shows an abnormal amount therein. This would indicate a large supply from some source—either from waste of the tissues, or from the excessive ingestion of highly-azotized food, to which latter cause we some time since alluded. Dr. Copland notices, in a comprehensive and satisfactory manner, the "Pathological Relations of Uric Acid and Urate of Ammonia" (*Dict. of Pract. Med.*); and M. Becquerel (*Sêmêiotique des Urines*) agrees with him in his views. Copland, referring to this, considers the chemical explanations offered by Liebig, in connection with certain of these pathological points, "opposed to clinical observation."[1]

Dyspepsia, with mal-assimilation of food and consequent deficient nutrition, or arrested cutaneous function and habitual costiveness, no less than obstructed excretion of the urine, may engender an excess of uric acid, and the latter may be retained in the blood. (Copland, *loc. cit.;* Chambers, *Digestion and its Derangements; et al.*) It is likewise true, conversely, that in depraved, deteriorated, and anæmiated states of the circulation, uric acid is diminished in the urine. If this ill-adjusted balance implies the throwing of an unusual quantity of the substance into the blood, the latter circumstance may have no small amount of influence, if not in causing, at least in continuing, the disorder of the blood itself and of the constitution generally. Gout occurring under such circumstances—as it is not very infrequently known to do—would be appropriately termed *atonic gout,* or what Dr. Todd (*Clinical Lectures*) terms "*asthenic gout,*" in contradistinction to his "sthenic gout," where the affection occurs in robust, well-constituted, and richly-nourished individuals.[2]

In reference to the dyspeptic condition of gouty patients, often so exceedingly troublesome, Dr. Chambers (*op. cit.*, American edition, 1856, pp. 294–95) refers rather scornfully to the influence of uric acid as a noxious element. He is remarking upon the tendency of the food to become acid after ingestion, and to lie unchymified—not "passing onwards." This state of things, so common in hereditarily gouty persons, Dr. Chambers is inclined to explain by considering its pathology "to be a slight flux of mucus, deficient gastric secretion, and yet a vigorous, sometimes even excessive appetite. Hence, they have not that check of failing desire for food which makes the meals of other invalids moderate, and eat more than their imperfect gastric juice can digest. This is a simpler, and, therefore, more probable explanation than the usual chemical talk about uric acid, &c., which might be substituted for it." It seems there is some fault in the working of the hidden *chemistry* of the body, however; and, although Dr. Chambers's explanation is doubtless very correct in reference to the influences and agencies of which he speaks, yet the overt action and manifestations of excess of uric acid, in the visible form of urate of soda concretions, sufficiently show the importance of the part it plays in the *tout ensemble* of gouty affections.

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[1] Dr. Copland does not believe that the presence of urate of soda in the blood of gouty patients precludes "the elaboration of a portion of the uric acid and its compounds, or the modification and metamorphosis of one or more of their elements by the kidneys." (*Dict.*)

[2] These two forms of gout, we conclude, are those termed by Dr. Druitt "*high*" and "*low*" gout. (*The Surgeon's Vade Mecum*, 1859.)

The original conclusions of Dr. Garrod, given in the admirable paper to which we have referred, were these:—

> "1st. The blood in gout contains *uric acid* in the form of urate of soda, which salt can be obtained from it in a crystalline state.
>
> "2d. The uric acid is diminished in the urine immediately before the gouty paroxysm.
>
> "3d. In patients subject to chronic gout with tophaceous deposits, the uric acid is always present in the blood and deficient in the urine, both absolutely and relatively to the other organic matters, and the chalk-like deposits appear to depend on an action in and around the joints, &c., vicarious of the 'uric-acid-excreting' function of the kidneys.
>
> "4th. The blood in gout sometimes yields a small portion of urea (no albumen being present in the urine)."

These conclusions were all duly sustained by analyses and experiments upon patients in University College Hospital; and the record of these demonstrations is at once satisfactory and highly interesting.

In respect to the supervention of gout in low and debilitated states of the system, to which allusion has previously been made, Dr. Garrod very clearly explains "two facts" then considered opposed to referring the pathology of gout to the humoral doctrines. We may say, *en passant*, that the humoral pathology seems the only reasonable mode of explaining the affection, and that, as may be distinctly perceived, it is coming more into favour of late, than it has been for a long time, in respect to many diseased conditions.

Dr. Garrod's remarks on the above point are:—

> "Any undue *formation* of this compound (urate of soda) would favour the occurrence of the disease; and hence the connection between gout and uric-acid gravel and calculi; and hence the influence of high living, wine, porter, want of exercise, &c., in inducing it." Then, speaking of the "two facts"—viz., *hereditariness* and the supervention of gout in *low states* of the system—he says:

in question is permanently injured [viz., the 'uric-acid-excreting' function], it will not require an excessive formation of the acid to cause its accumulation in the blood." (*Loc. cit.*, pp. 93, 94.)

Dr. C. J. B. Williams (*Principles of Medicine*), referring to the fact that gout had been generally admitted, by inference, to depend on the existence of an excess of uric acid in the system, chronicles Dr. Garrod's experiments and analyses, which, as we have stated, were first made on patients under Dr. W.'s care, in hospital. He says:—

> "Gout, and the commonest kind of urinary gravel are now generally considered to depend on the production in the system of an excess of lithic acid." (*Loc. cit.*) The case from experiments upon which Dr. Garrod was first enabled to draw his reliable conclusions, "was one of chronic gout; and further illustrated the pathology of the disease, by a total absence of lithic acid in the urine, until during the exhibition of colchicum, when its characteristic crystals appeared under the microscope."

Sufficient testimony, it would appear, has been adduced, to render the position tenable which ascribes the gouty paroxysm to an excess of lithic acid, circulating in the blood, and finally deposited in various parts of the body.[1] It does not seem to devolve upon us to describe the phenomena of a fit of the gout—expected as we are, merely to signalize the "effects" of retention of the various elements of the urinary secretion in the blood, we should strictly confine ourselves to such specification, and to the adduction of the best evidence afforded in its support.

In the first place, then, we may refer the phenomena of gout, more or less completely, to that disorder of the eliminating function of the kidneys, which permits the latter organs to refuse the excretion of uric acid. The latter substance is then necessarily thrown into the circulation, and its tendency—under the circumstances—is to accumulation in the blood. As it accumulates, it is converted, most commonly, into urate of soda, and the deposition of the latter substance upon and into various tissues of the body is a *quasi* vicarious discharge of the uric acid, not excreted by its legitimate channels, the kidneys. This condition is accompanied by the objective phenomena of gout, viz., pain, of an exquisitely acute and torturing character; feverishness, dyspeptic symptoms, and general *malaise*;[2] at the close of the paroxysm, tense, shining, and often excessive swelling of the affected part; finally, entire remission of the symptoms, and better health than before the attack—owing, of course, to the elimination of the *mate-*

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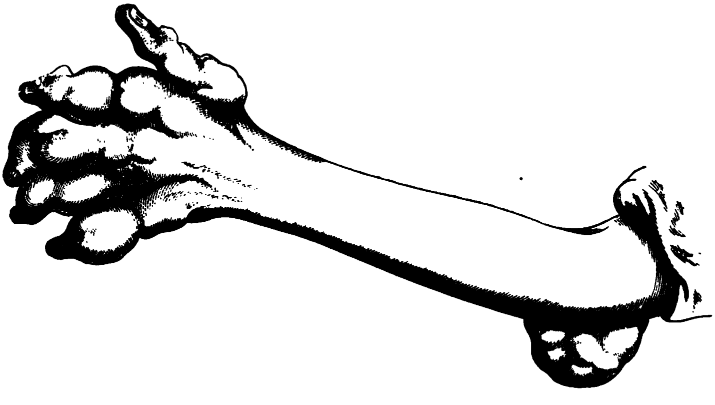
[1] See Appendix, Note B.

[2] "An impure state of the blood, arising principally from the presence of urate of soda, is the probable cause of the disturbances which not unfrequently precede the seizure, and of many of the anomalous symptoms to which gouty subjects are liable." (A. B. Garrod, *op. cit.*, p. 341.)

his appetites; the fact of hereditary predisposition, or the contrary; and whether the management of the initial attack is judicious, or otherwise. By renewed attacks—chronic gout—the system of course becomes more shattered, less capable of resistance, and less amenable, too often, to remedies. Locally, a variable, often an excessive, amount of injury supervenes. It is at these periods that the lithate of soda—the morbific material—is deposited in various places—principally about the smaller joints. Nature, in her efforts to eliminate this material by other channels than those which are the legitimate ones, does the best she can, but often terribly cripples the subjects of this trying affection (see Fig. 2). Connected with this chronic form of the complaint, we are apt to notice the most troublesome combinations of dyspeptic ailments; and in these the condition of the patient becomes the most unpromising possible, both from the local and from the systemic difficulty. As Dr. Williams states, the uric acid, in such cases, "seems to be engendered in great abundance, and although thrown off in large quantities in the urine for an indefinite period, yet never leaves the body free. Such cases are commonly either hereditary, or those which have been rendered inveterate by intemperate habits, or neglect of proper treatment." (*Op. cit.*)

Fig. 2.



Elbow and Hand deformed by Gouty Enlargements.—From Dr. Garrod's work (Nature and Treatment of Gout.)

Sequelæ of Gout.—Considering gout as one of the affections ascribable to the retention of uric acid in the blood, let us inquire what are the principal subsequent results. These may, of course, be properly referred to the same cause, as "morbid effects."

We have seen that symptoms of general febrile disturbance, which are of course accompanied by nervous apprehension, fretfulness, heat of skin, decline, especially—with hypochondriacism, cramps, flatulence, diarrhœa, but more commonly costiveness (Watson), and more or less general and indescribable *malaise*, both precede and accompany gouty attacks. The dyspeptic symptoms may long remain; although, with care, they may be made sooner or later to disappear.

One of the most serious sequelæ of gout may be considered that wherein the kidneys are affected. Perhaps we may best describe the state we wish to indicate, by terming it the result of a sort of *recoil* upon the kidneys, of the antecedent morbid action in the economy. This is of course entirely the opposite condition of that obtaining when the kidneys fail to eliminate the uric acid, *i. e.*, when their "uric-acid-excreting function" is suspended. In the latter condition of things, we have the blood-disease, the results of which we have sketched above; but when the uric acid begins again to be excreted by its natural passages, the kidneys are very likely to be more or less irritated in the process. There may then be violent pain (*nephràlgia*), and nephritis or true inflammation of the substance of the organs may occur. Fully as unfortunate is that state when there is such an amount of uric acid as to be thrown down from the fluid part of the urine—the latter not being sufficient to hold it in solution, and thus carry it out of the body—when it is exceedingly apt to become concreted in various parts of the urinary passages—thus producing obstructions more or less seriously endangering health, and vitiating, in different degrees, the integrity and usefulness of the organs involved. Permanent irritation may thus be maintained; or serious and fatal inflammation be set up; and concretions may be found in the urinary bladder, which will call for surgical interference for their removal.

Dr. Williams (*op. cit.*), referring to the renal irritation frequently caused in these cases (p. 130, American edition, foot-note), says: "I have in several instances found in the cortical and tubular structure of the kidney, clustered crystals of lithic acid, which, under the microscope, exhibited such sharp angles and dagger-shaped projections, as would afford an easy explanation of the pain, inflammation, and hemorrhage, often attendant on an attack of renal gravel, even when none is obvious in the urine." The same writer reminds us (p. 187), of "the proximity in composition between lithic acid and urea," and that it is probable, according to Liebig, that the former may be converted into the latter. He likewise calls attention to the fact that both gout and rheumatism may give rise to fluxes and catarrhal affections, as oliguria does. Rheumatism and Bright's disease are also, often, nearly related. In respect to this fact, Dr. Garrod announced the following opinions and conclusions, in his paper already quoted (*Med.-Chir. Transactions*, vol. xxxi.), "Blood from patients suffering from Bright's these analyses appear to show that—

"1st. Uric acid is always present in the blood in albuminuria. The quantity, however, greatly varies: when the functions of the kidneys are much impaired, it exists in quantities almost as great as in gout; in other cases its amount is small, but it usually exceeds that found in ordinary blood.

"2d. Urea always exists in large quantities in this blood (a fact which has been long since proved), and no relation is found between the amounts of urea and uric acid.

"3d. The kidneys are always deficient in their power of throwing off urea; but with regard to the uric acid, their excreting function may be impaired or not." (*Loc. cit.*)

We thus see what serious disturbances may arise in the system by a perverted condition of secretion, arrest of excretion, and attempts at vicarious elimination of a product which must, in order to the preservation of health, be discharged from the body. The diseases thus produced come clearly under the head of *disordered vital chemistry.* Thus, when the above vital functions are weakened, or totally disabled, there must be not only general disturbance, but, after a time, some special manifestation of disease, and the results of vitiated secretion, decomposition, and over-worked and irritated organs.

The *contracted kidney*—called, by the late Dr. Todd, "the gouty kidney"[1]—and which, as the term he has given it implies, he considered due to the effects, at once irritant, inflammatory, and destructive, arising from gout, we may mention as a result primarily dependent on disorder of the "uric-acid-excreting" function. Dr. Todd has given satisfactory proof (*Clinical Lectures on Certain Diseases of the Urinary Organs*) from cases of patients, of the existence of this form of renal disease. He mentions, also, that many might be inclined to refer it to advanced Bright's disease; but he has signalized it in those who he believes never had that affection. The kidney is shrunken, "and its structure condensed—a condition which, while it may also occur in other states of the system, is peculiarly apt to be developed in the inveterate gouty diathesis." (*Loc. cit.*, p. 313.) In one case, necroscopy disclosed hypertrophy of the heart with dilatation—partly due to incrustations on the mitral valve—hardened, condensed, and somewhat contracted liver—the Glissonian capsule being hardened and thickened. The morbid alteration in the latter organ is explained partly by the intemperate habits to which the patient was addicted, "but partly likewise by the share which the liver had in the elimination of the morbid poison of gout." This latter result, which is not infrequent, it is important to notice, as one of the secondary effects of the diverted and retained urinary element. The kidneys in this patient were very much contracted, being hardly one-third of their natural size; they were granular and shrivelled upon their surfaces; the investing capsule was apparently denser and whiter than usual, and was easily detached from the glandular surface. Diminution of the cortical renal substance was the source of the decrease in the size of the organ; two-thirds being estimated to have disappeared. The granulations were noticed likewise upon the cut surface. Dilated and scantily-lined *tubuli uriniferi* were observed on microscopic inspection; from some of them all the epithelial lining had vanished; others were collapsed, folded, and crumpled up; and looked like "fascicles of fibrous tissue." A few fatty epithelial cells were detected in certain *tubuli;* and others of the latter were seemingly healthy, especially those in the pyramids of Malpighi. Dr. George Johnson[1] has described, very minutely, this condition of the kidney, and particularly notes the changes which supervene in the vascular system of the gland. In another instance, Dr. Todd has recorded the discovery, in an inflamed "gouty kidney," of "*opaque streaks of deposit of lithate of soda*" in some of the renal cones. These streaks took the direction of the tubes, and certain of the latter were probably occupied by them.[2] We may well exclaim with Dr. Todd, as we reflect upon these vital manifestations and post-mortem revelations—

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[1] A term objected to by Dr. Barclay (*op. sup. cit.*); who, however, very distinctly recognizes the close connection between gout and renal disease. Valleix, writing in 1853, would not admit that special form of nephritis which is referred to the gouty diathesis.

> "How strikingly do these consequences of the long continuance of the malady comport with the humoral view of the pathology of this disease! Not only are those parts which the morbid matter of gout is most prone to affect, materially damaged, but likewise the emunctories through which the poison would make its escape out of the system—the liver and kidneys: these organs have become poisoned by the morbid matters which have escaped, or tried to make their escape from the system through them; and, therefore, it is natural to expect a considerable change in their nutrition."

It is notorious, however, that in most, if not all, of the *metastases* of gout, there are no traces of morbid action upon the organs affected by the repercussion of the disease. The reason of this doubtless is, that when a fatal result occurs in this manner, the morbid action lasts too short a time, notwithstanding its violence, to leave structural traces. Probably a true *spasmodic* action often destroys the patient, in the thoracic and abdominal varieties of retrocedent gout. It is, however, very likely that in many cases of sudden death from these causes, the vital organs have been previously weakened by disease of some sort; and in many cases chronic gout has inflicted a certain amount of injury, for, as we have already seen, the behind it.

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[1] On Diseases of the Kidney.

[2] This appearance is also noted by Dr. Garrod, who saw "streaks of white matter at the apex of each pyramid and running up in the direction of the tubuli. Kidneys pale and contracted; cortical portion shrivelled." (p. 199.)

After gout in the *stomach*, Dr. Todd signalizes a "dilated and flaccid state of the organ" as existing, and this is the more marked in proportion as the attacks have been frequent.[1]

In addition to the abundant and often astonishingly copious deposits of the urate of soda into and around the joints, that salt has been found to cover and even to penetrate into the texture of the cartilage investing the affected joints (Watson), and to insinuate itself into the substance of tendons and ligaments (Dr. Wm. Budd). A curious locality is at other times chosen by it—viz., under the skin covering the cartilages of the ears. It has been remarked also over the cartilages of the alæ nasi (Todd).[2] Pus sometimes forms around the variously located depots of urate of soda, and occasionally the discharge of this liquid is quite abundant. Generally speaking, also, the joints of the hands and arms exhibit more plentiful deposits of the urate than those of the lower extremities, except in some forms of acute sthenic gout, when the reverse may be observed. The one, that we hardly need do more than allude to it as a "morbid effect" of the disease. The fact, moreover, has already been made sufficiently prominent.

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[1] Op. cit.

[2] Dr. Garrod (op. sup. cit.) states that "sometimes small nodules of urate of soda are found upon the eyelids, especially the lower, now and then in the integuments of the face." He also refers to the great care which is necessary in ascertaining the precise nature of the "white-looking deposits" often occurring about the eyelids and face. Dr. H. Barker saw them on the nose. Dr. Garrod has "observed a true gouty deposit as large as a split pea, apparently attached to the fibrous structure of the corpus cavernosum penis." (p. 86.)

In relation to gouty affections of the eye and ear, Dr. Garrod further remarks: "A form of ophthalmia connected with gout has long been noticed." He adds that it is liable to be confounded with rheumatism, when that is directed to the ocular region. Cases of ophthalmia evidently connected with the gouty diathesis have been observed by Dr. G.; these were instances of conjunctivitis and sclerotitis. "Gouty iritis is also said to occur." The nodules found upon the cartilages of the ear have been mentioned. "Deposits are not unfrequently found upon the drum of the ear, and have been especially pointed out by Mr. Toynbee, but I have failed to discover a trace of uric acid in several examinations of them. Whether they are ever connected with gouty inflammation, is at present a matter of uncertainty; they should especially be sought for in gouty subjects in whom the joints are much affected with chalk-stones, for if not found in such cases, it is not probable that they would occur in others." (pp. 515, 516, op. cit.)

Accomplished aurists have pointedly alluded to the connection between gouty and rheumatic affections and deafness. Mr. William Harvey (The Ear in Health and Disease, London, 1856) specially considers this subject; and we have heard him insist upon the frequency of the connection, whilst observing his aural practice.

In his elaborate work on The Diseases of the Ear, just published (London, 1860), Mr. Toynbee refers to the subject, and furnishes interesting illustrations of the reality of the connection, as observed by himself. He says: "The poison of *gout* may also give rise to deafness and other peculiar symptoms in the head." (See the work cited, page 362, English edition.)

RHEUMATISM.—Nearly related to gout is the disease known by the term *rheumatism;* an affection which, like its *congener*, may be *acute* or *chronic*, and is characterized by very similar constitutional symptoms and by many local phenomena of like nature, while yet there are several striking points of difference. Thus, we observe indications of irritative action and of inflammatory states of variable severity; fever, anxiety, restlessness, chills, with full, quick and sharp pulse; gastric and intestinal disturbances; thirst, white tongue, foul breath, and acid eructations. Locally, there is heat, pain, and tense, or sometimes doughy, shining redness, with swelling around certain joints, and often affecting neighbouring tissues, as the muscles, tendons, &c. By preference, the larger joints are attacked in contradistinction to gout, which, as we have seen, fixes upon the smaller. There is also the remarkable and very distinctive symptom, or rather local manifestation, of *acid perspiration*, often very profuse and offensive. The latter is apparently the corresponding fact, so to speak, to the local appearance of urate of soda in the tophaceous deposits in gout; for, in true rheumatism, nothing of the sort occurs; in *rheumatic gout*, as will be seen, there is an analogous deposit.

From what we have already indicated, it is not difficult to see a great resemblance between gout and rheumatism; they have indeed been denominated *"first cousins."* The first and most important question for us, concerning rheumatism, is—and it is an inquiry of great practical interest—*does it depend upon excess of uric acid in the blood, and its retention therein?*

The latest views of the pathology of the disease seem to give a directly *affirmative* answer to this question; and, of course, under this aspect of the subject, it devolves upon us to enumerate the affection and its results amongst those "morbid effects" of retention in the blood of the urinary "element" we are now examining. It should, however, be distinctly premised, that many researches and much close study and observation are yet required in order to enable us positively to declare uric acid or any of its products to be the *materies morbi* in rheumatism. Observers, however, at the present day, at least begin to speak with more confidence and decision upon this point. In the first place, we find it more than ever common for systematic writers on medicine to consider gout and rheumatism under one head; often in one chapter. Next, if we examine the language employed in discussing the yet unsettled question as to the *essential cause* of the left open to doubt—most authorities not fully compromising themselves. We will refer to a few of these opinions. Dr. Barlow (*Manual of the Practice of Medicine*, 1856) says:—

> "The external cause [of rheumatism] is generally exposure to cold, especially when producing repressed perspiration. Its internal or essential cause seems to be an abnormal condition of the blood, which contains always an excess of fibrin and of uric acid: the latter is probably the *materies morbi* or peccant matter." (p. 130, *op. cit.*)

Dr. Bennett (*Clinical Lectures on the Principles and Practice of Medicine*, American edition, 1858) begins his remarks upon the General Pathology of Rheumatism and Gout, as follows:—

> "The present theory with regard to these affections is, that they are both connected with an increase of lithic acid in the blood. In rheumatism, this is dependent on excess of the secondary, and in gout on excess of the primary digestion." (*Op. cit.*, p. 909.)

The latter author also refers to the fact that a considerable amount of *lactic acid* is excreted from the skin, as was taught by Prout, and mentioned by Todd, Watson, and others of note, who have carefully studied the subject. Hitherto, the tendency seems rather to have been to ascribe the morbid phenomena of rheumatism to an excess of the last named acid in the system. Dr. Prout, in the fifth edition of his celebrated work on *Stomach and Renal Diseases*, refers pointedly to this explanation, as being his own belief. While mentioning in a foot-note (p. 549) the opinions of Dr. Garrod as to the relations of uric acid to gout and rheumatism, he says: "In various parts of this work I have spoken of lithic acid as being characteristic of gout, and the lactic acid of rheumatism. At any rate, I agree with Dr. G. that lithic acid has little to do with pure rheumatism; though it is often present in what is called rheumatic gout." In the latter affection—which is understood to be that variety of gout which attacks all the joints, indiscriminately, and for which Dr. Todd prefers the name of "*general gout*"—it is natural to believe that the chief morbific agency is uric acid, or a salt from it. It has, however, as we previously stated, until somewhat recently, been the persuasion of the majority of observers that lactic acid held that relation to rheumatism, which it seemed plausible to assign to uric acid in reference to gout. In his last edition (1857), Dr. Watson says, in the course of a remarkably clear and accurate *resumé* of the distinctions existing between gout and rheumatism (*op. cit.*, vol. ii. p. 761, English edition): "Gout is often, rheumatism is never, associated with chalk-stones; and conformably with this distinction, Dr. Garrod has not present in that of rheumatic patients."[1]

The manner in which Dr. Todd (*op. sup. cit.*) refers to the method pointed out by Dr. Garrod for detecting uric acid in the serum of the blood, in gouty cases, seems decidedly indicative of his own views as respects the existence of uric acid in excess in the blood in gout and not in rheumatism; and in this connection, we are glad of an opportunity to give the method of Dr. Garrod, above referred to. Dr. Todd says:—

> "Dr. Garrod has made out a positive physical character of gout, which may be regarded as surely diagnostic of that disease from rheumatism. It consists in the discovery of uric acid in the blood-serum or the blister-serum. And his process is ingenious, and so simple that any one may use the test, however little accustomed to chemical manipulation. A little serum is put into a watch-glass, and to it are added five or ten drops of acetic acid. In this acidulated serum a small skein of worsted is laid, and the watch-glass is set aside under cover to protect it from dust. After a few hours, the crystals of lithic acid, if it exist, will be found adhering to the threads."[2] (*Op. cit.*, pp. 408–9.)

Dr. Henry William Fuller, of London, Assistant Physician to St. George's Hospital, in his very scientific and able treatise on *Rheumatism, Rheumatic Gout, and Sciatica*, published in 1852, takes the ground that *lactic acid* is the *materies morbi* in rheumatism. He thus falls in with the opinions of Drs. Prout, Todd, Williams, and others, who so believed, although not positively asserting the fact as indisputable. Dr. Fuller considers the cause of the disease to be a poison in the blood, and which is generated in the system as the product of a peculiar form of mal-assimilation—of vicious metamorphic action. This poison it is "which excites the fever, and produces all the pains and local inflammations which are often found associated in an attack of rheumatism." (*Op. cit.*, p. 28.) He then points out the fact that although the fever may be increased by the occurrence of the local inflammations, "it is essentially independent of them," and often is well developed before they begin. If the virus is in small quantity in the blood, then only slight wandering pains are produced;

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[1] Speaking of Dr. Prout's belief in regard to the *lithic* and *lactic acids*, and their relations to gout and rheumatism, Dr. Watson relates certain experiments, by Dr. Richardson, upon animals. Lactic acid introduced into the peritoneal cavity of a healthy cat, produced irregular cardiac action in two hours. The animal was found dead the next morning, and no peritoneal inflammation was discovered, but "marked endocarditis of the left chambers of the heart. The mitral valve was inflamed and thickened, and covered on its free borders with firm fibrinous deposits. The whole inner surface of the ventricle was highly vascular." Similar results were observed in a dog experimented upon in like manner. No textural alterations were found in the joints.

[2] In Dr. Garrod's late work (*Gout and Rheumatic Gout*) we find this process much more elaborately described. See pages 110–113, *op. cit.*

We have previously cited the authority of Dr. Garrod in reference to the morbific agency in gout and rheumatism;[1] and in his late work, we find him reiterating his views, and pronouncing the urate of soda "*pathognomonic*" of gout. Some of this author's conclusions thus lately arrived at, or rather confirmed—for such, we believe, has always been his doctrine—are so positive and so much to the point for our present purpose, that we quote them. His analyses show that "healthy blood contains the merest trace of uric acid or urea, so small as to be in general undiscoverable, except by the most minute and searching chemical examination, and not always then.

> "That, in gout, the blood is invariably rich in uric acid, which exists in the state of urate of soda, and can be separated from it, either in the form of the crystalline salt in acicular needles, or as rhombic crystals of uric acid.
>
> "That, in acute rheumatism, the blood is free from uric acid, or, at least, contains no more than in health.
>
> "That the perspiration seldom contains uric acid; but that, in gout, oxalate of lime may be crystallized from it, as also from the blood."[2]

In the above expressions of opinion, founded on careful analysis, we find Dr. Garrod distinctly declaring that the blood is free from uric acid, or only contains a normal amount thereof; he therefore does not consider that acid the cause of rheumatism.

Such are some of the opinions to which we referred; and while, in view of the existing difference in the decisions of equally eminent men upon this point, we cannot look upon the pathology of rheumatism as by any means definitively settled, it seemingly devolves upon us to consider the disease as a condition referable to excess of uric acid in the system, in deference at least to the opinion of many of the latest observers, whose position, judgment, and opportunities for the accumulation and weighing of evidence are such as to entitle their announcements to the greatest respect. In this regard, however, as much can be said for those who hold the opposite views, or who do not fully compromise themselves; but we shall be quite safe, at least, in discussing the question according to the plan above announced. Our own conviction, hitherto, has always been wholly in favour of the *lactic acid* theory; and, within a day or two, having put the question to a highly-cultivated and well-informed medical friend—"What do you consider the *materies morbi* in rheumatism to be?" his reply was, after a

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[1] "The Nature and Treatment of Gout and Rheumatic Gout."

[2] In giving these opinions of Dr. Garrod, we followed the statement furnished in the *Lancet* of December 24th, 1859, not then having seen Dr. G.'s work. The account is by the Reviewer, condensed from the book itself. We have lately, however, had the volume at our disposal, and can testify that it is a most satisfactory, complete, and erudite treatise.

Whatever the fact may be, it is clear that the fault of *deficient excretion* is equally active in rheumatism as in gout; the former is as distinctly a blood-disease as the latter.[1] The deranged excretory function ("Uric-acid-excreting"), however, chooses a different field for the manifestation of its disorder or impairment; the disarranged balance between the excess of acid and the excreting power being as evident in one as in the other. Dr. Bennett (*op. cit.*) writes very clearly and comprehensively on this point. He remarks: "In both diseases there is an undue balance between the excess of lithic acid and the power of excretion—in rheumatism by the skin, and in gout by the kidney. This pathology serves to explain the similitudes and differences existing between the two affections. In both there is a certain constitutional state dependent on deranged digestion, during which, exciting causes occasion local effects."

He then signalizes the fact that in rheumatism the *exciting* causes are those of a depressing nature, and are usually exerted upon the poorer classes. The chief provocatives of rheumatism, as is well known, being cold and wet, bad and insufficient food, and hard labour. As we have already set forth, precisely the opposite immediate causative elements are active in gout, *i. e.*, luxurious and intemperate diet, indolence and self-indulgence of all kinds. Dr. Fuller's idea—and which is, doubtless, that of every reflecting and intelligent practitioner—is, that the morbid material acting in the blood, is often, if not nearly always, the *sole* cause of rheumatism—secondary or exciting causes not coming at all into play, or proving ineffective, if brought to bear on the system. They are only promotive agencies, not causative elements.

It will not be expected of us, we conclude, specially to detail the course of rheumatic fever, or of chronic rheumatism. Indeed, with the present undetermined state of the pathology of the disease, we might perhaps have deemed it justifiable to withdraw the disease from the category of the "morbid effects" of retention of an element of the urinary secretion in the blood. It could hardly, however, be other than an omission of some moment, had we not carefully examined the present belief on the subject; and, having done this with considerable research, we place in due order the names of all the authors of most eminence in regard to the subject, within the last few years, whose works we have been able to consult. Their opinions are expressed with more or less positiveness; some only implying their belief, others boldly asserting it.

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[1] "In truth, acute rheumatism is a blood-disease. The circulating blood carries with it a poisonous material, which, by virtue of some mutual or elective affinity, falls upon the fibrous tissues in particular, visiting and quitting them with a variableness that resembles caprice, but is ruled, no doubt, by definite laws, to us, as yet, unknown." (Watson, *Practice of Medicine*, vol. ii. pp. 738–9.)

LACTIC ACID.		URIC ACID.	
Dr. Prout	(1848.)	Dr. Barlow	(1856.)
" Fuller	(1852.)	" J. H. Bennett	(1858.)
" Todd	(1857.)	" Copland	(1858.)
" Watson	(1857.)	" Thudichum	(1858.)[1]

With respect to Drs. Thudichum and Golding Bird—the latter of whom might have been ranged with the former in the above table—their opinions are inferred from expressions in their works, such as we quote in a footnote.[2]

It may here be added that Dr. Prout intimates it to be a very supposable and plausible doctrine that the phenomena of rheumatic gout—which, by the way, both he and others pronounce very difficult to relieve—may be explained by the fact of the concurrent action of both lactic and lithic acid in the system. This form or combination of disease requires to be described more at length, as being less familiar than rheumatism, and presenting more novel points for inquiry.

RHEUMATIC GOUT.—We have already referred to this affection, which presents a singular combination of the characteristics of rheumatism and gout. Without resembling either, as a whole, it partakes, seemingly, of the nature of both. Unlike gout in general, it attacks the weakly individual as well as the strong, and quite as readily; or else those who are robust, when either physically or mentally depressed. In this malady the analogy of the two diseases is most apparent; or rather, their dependence upon a

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[1] Dr. Garrod might, by inference, be placed in the left-hand column; since, although he does not, so far as we have been able to ascertain, say that rheumatism depends on the presence of an excess of *lactic* acid in the blood, he demonstrates the absence of *uric* acid in the cases he has examined, and evidently does not consider it, in any wise, dependent thereon. (See his late work on *The Nature and Treatment of Gout and Rheumatic Gout.*)

[2] "In the two allied affections, gout and rheumatism, exclusive of the many neuralgic diseases popularly referred to the latter, a remarkable tendency to the formation of an excess of uric acid, both pure and combined, occurs." G. Bird, *Urinary Deposits*, English edition, by E. Lloyd Birkett, M. D., 1857, p. 150.

"As a question clearly put is half the answer, we may be permitted here to consider what proximate conditions of the system a rise or fall in the quantity of uric acid beyond the normal limits is likely to indicate. A deficiency may be due to a diminished production in the system, as in anæmia, or to retention, as in certain stages of gout and rheumatism. It is at least questionable whether the retention is *always* due to diseased action of the kidney. Any disease, however, which interferes with the secreting power of the kidney by changing its structure, such as Bright's disease, is certain to cause retention of uric acid in the blood, in proportion to the retention of the other constituents of urine. (Scarlatina seems to make an exception. * *.") Thudichum, *op. cit.*, p. 95.

Garrod, in his work just published,[1] does not incline to the idea that this affection is actually a combination of gout and rheumatism. He prefers, moreover, to employ the term "*Rheumatoid Arthritis,*" and remarks: "If we agree to name a disease simply from its external characters, then I admit that the term rheumatic gout is not inappropriate; but if we advance further, and have regard to more intimate pathology, then I deny the propriety of the name: acting upon the former principle, we should be equally justified in calling some cases of scarlatina or measles by the compound term of rubeolo-scarlatina, and we know that these diseases were not separated two centuries ago * *." "Although unwilling to add to the number of names, I cannot help expressing a desire that one might be found for this disease, not implying any necessary connection between it and either gout or rheumatism. Perhaps *Rheumatoid Arthritis* would answer the object, by which term I should wish to imply an inflammatory affection of the joints, not unlike rheumatism in some of its characters, but differing materially from it." (*Op. cit.*, pp. 533–4.) Dr. Garrod also refers to the fact that but few authors recognize any existing combination of gout and rheumatism, many even strongly oppose such a doctrine. He mentions Boerhaave, Van Swieten, Cullen, Heberden, and Watson, as not alluding to such a connection or fusion, and quotes Sir C. Scudamore, as saying "that the textures which have been long affected with gout, become so much weakened as to be very susceptible to vicissitudes of temperature; and in this way the general disorder may partake of rheumatism. It was only thus that he could attach any propriety to the very common expression *rheumatic gout.* It would appear that the term is often made use of, but seldom attempted to be defined with precision." (*Op. cit.*, p. 527.)

The affection has been known by various names. Thus Dr. Haygarth styled it "*Nodosity of the Joints;*" Cruveilhier, "*Usure des Cartilages Articulaires;*" Dr. Adams, of Dublin, "*Chronic Rheumatic Arthritis.*" Dr. Garrod, who mentions the above designations, also says: "It has sometimes received a name dependent on its situation; for example, rheumatic gout, when the wrists, hands, and feet are affected; chronic rheumatism, when in the shoulder, elbow, or knee, either singly or simultaneously; and *morbus coxæ senilis,* when located in the hip. Occasionally it assumes an acute, or rather subacute, character, but more generally it is chronic throughout." (p. 533.)

Neither *sex* nor *condition* in life seems to have any influence in procuring immunity from this disease. According to Dr. Adams, the hip-joint is most often affected in males; in females, the wrists and hands. He found

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[1] The Nature and Treatment of Gout and Rheumatic Gout. By Alfred Baring Garrod, M. D., F. R. S., Fellow of the Royal College of Physicians, Physician to University College Hospital, etc. etc.; London, Walton and Maberly, 1859.

Brodie considers it most common in the higher classes. This diversity of opinion, Dr. Garrod explains by referring it to the "difference in the class of cases more prominently brought under each surgeon's notice." (*Op. cit.*, pp. 534–5.)

The *main characteristics* of the disease may be grouped as follows: Pain, of a migratory nature, and which is often very severe and obstinate. It is sometimes aggravated at night, and also by heat. (Garrod.) Motion is extremely painful to an affected joint, especially after prolonged rest. There is notable frequency of recurrence, and predilection for the smaller joints. The joints attacked become, after a time, swollen; fluid is effused in considerable quantities into the cavities of the joints, and fluctuation is often perceptible. The ratio of helplessness is, of course, in relation with the number of joints crippled; generally, none of the articulations escape, when once any of them have been invaded. There is usually but little accompanying febrile excitement and constitutional sympathy; although this depends, very distinctly, upon the number of joints attacked; that is, upon the extent, or degree of universality of the disease. (*Auct. cit. et al.*)

Complications.—Cerebritis, pleuritis, inflammation of the eye. The latter is comparatively rare; all the ocular tissues may be affected; generally, however, if the patient have treatment, the choroid coat and the iris escape. Exhausted and shattered constitutions are those most obnoxious to ocular inflammation in connection with rheumatic gout. (Fuller.)

Results.—Thickening and permanent enlargement of the structures forming, and (less frequently) of those surrounding the joints; occasionally, there is cuticular desquamation, as in gouty cases. In the chronic form, which, as we have stated, is most commonly observed, the articular cartilages are affected, the ligaments about the joints are stretched, and the ends of the bones are irregularly enlarged. The synovia subsequently becomes absorbed, and the capsular membrane is left much thickened. The *ligamentum teres* of the hip, and the tendon of the biceps are sometimes destroyed, and even completely removed. Not only the articular, but the inter-articular cartilages are absorbed; this is observed in the knee-joint, the wrist and the lower jaw. (Garrod.) When the disease has been very prolonged and severe, the synovial membrane becomes not only thickened, but droops into the articular cavity; or, as Dr. Fuller points out, "a dense, ligamentous substance, resulting probably from some peculiar alteration in the synovial membrane, is seen interposed between the articulating surfaces; or small irregularly shaped cartilaginous bodies are found, either loose within the joint, or attached to it by pedicles formed of thickened synovial membrane." Sometimes these excrescences are bony; and others of a vascular nature likewise exist. (Garrod, *op. cit.*) The opposite surfaces of the bones forming the joints, being denuded by chronic wasting of the cartilages, and rendered smooth by attrition upon each other, are found to be white, glistening, and ivory-like in appearance. The latter condition, we conclude, is that observed in what is termed "dry chronic arthritis"—*Arthrite chronique sèche* of the French writers. We have had the opportunity of witnessing this alteration in several instances; the state is that known as *eburnation*. In specimens which we have seen, the change of texture was chiefly marked in the track of the *greatest attrition*, in the affected joint; a fact noticed particularly by Dr. Garrod. (*Op. cit.*)

> "The denuded surfaces become partly worn away, and a smooth enamel is formed by the mutual action of the bones on each other, and around the articular surfaces thus acted upon bony vegetations arise.
>
> "In most joints, after the fluid has become absorbed, a crepitus is felt on movement from the rough surfaces grating against each other." (p. 540.)

There is, in certain instances, a pulverulent deposit, usually consisting of lithate of soda, but containing also, at times, lithate of potash, ammonia and lime, chloride of sodium, phosphate and carbonate of lime. This lightly incrusts either the entire surfaces of the affected joints, or only portions thereof; and it may pervade their solid structures.

Although this deposit is identical, or nearly so, with that of gout, and occurs alone in those cases of rheumatic gout most nearly resembling genuine gout, yet, says Dr. Fuller, "I cannot therefore admit the conclusion that the existence of such deposit is of itself sufficient to mark such cases as examples of true gout." (p. 331.) The reasons he assigns for this opinion are, briefly: 1. The occurrence of these cases in "thin, spare persons of temperate habits," who have had rheumatic rather than gouty symptoms; 2. The difference in form and situation from the chalk-stone deposit of true gout; 3. The disease occurs, often, in those who formerly have had pure uncombined rheumatism; and these persons sometimes exhibit the well-known external traces of that disease. This author distinctly avows his belief that rheumatic gout is a true combination of the two diseases whence it derives its name; and when, on dissection, one joint is found to present most evidence of the gouty, and another most of a rheumatic element having been at work, he explains this by supposing that more of one influence was in force during the time such a joint was affected; and the other result rests upon similar action from the opposite influence. Dr. Garrod, who, as we have already stated, does not consider the affection to be a compound of gout and rheumatism, admits, notwithstanding, its greater resemblance to rheumatism than to gout; but he believes that much harm has been done practically, by confounding it with either gout or rheumatism.[2]

[1] Fuller.

[2] We take this opportunity to refer those interested in these subjects, to the elaborate and interesting treatise of Dr. Garrod, which we have designated above. The differential diagnosis of gout and rheumatism is clearly set forth, and the work is fully illustrated by tables, plates, etc.

Such, then, are the principal results—if we adopt the theory received, as we have seen, by so many reliable observers, viz., that rheumatism depends on retention of uric acid in the blood—of this poisoning of the blood by the undue presence of the *materies morbi* in the system; and both in this and the previously considered affection (gout) we have a series of symptoms indicative of the great extent to which the infection of the blood sometimes attains; and also ocular evidence, both during life and after death, of the power and virulence of the poison.[1]

We have not treated of the occurrence of *metastasis* of rheumatism under a separate head, because the chief danger in this light is of the *heart* being affected, and we have already pointed out the frequency of such attacks, and the necroscopic phenomena. Sufficient allusion, we believe, has also been made to the occasional transfer of the affection to other organs. The *sequelæ* of the disease have likewise been incidentally mentioned under the head of *results* and *consequent diseases.* It is, however, not supererogatory again to refer pointedly to the extreme danger which environs those who, during rheumatic fever, have also had heart disease. Such persons, even if apparently entirely recovered, *are never to be considered out of danger*, and they require, of course, due warning from their physicians, and the exercise of great discretion on their own part, in order that they may be fully aware of their insecurity, and able, so far as is possible, to guard against a return or re-awakening of their formidable malady.

We have thus endeavoured to present the chief phenomena, resulting directly and also secondarily from retention of uric acid in the blood. Whilst the manifestations of *gout* and *rheumatism* have been, of necessity, prominent, the reader will not have failed to remark the lengthy list of antecedent, concomitant, and subsequent, ailments, seemingly more or less dependent upon that morbid influence which, by common consent, is allowed to be the active promoter, and, we may say, the originator of the disease. From the slighter derangements of the general health, through all the phases of dyspeptical disorder, to the agonizing paroxysms of gout and rheumatism, their *sequelæ*, exceedingly dangerous metastases and disastrous ravages upon the external form, both as to appearance and freedom of motion; and finally in the *post-mortem* evidences of its activity, do we not seem to recognize the presence and morbid power of that

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[1] It should be stated that the testes, as well as the skin, periosteum and aponeuroses are occasionally affected, either concomitantly and acutely, or subsequently and in a more chronic manner. Dr. Fuller and others have enlarged upon the predilection of rheumatism for "the white fibrous tissue." The former author refers to the mention by Dr. Watson, of rheumatism of the articulation of the jaw, and also of that of the membranes of the spinal cord by Dr. Copland and others. (*Op. cit.*, p. 46.) We need hardly refer to the fact of the frequent association of rheumatismal attacks—in predisposed subjects—with gonorrhœa.

"element of the urinary secretion" we have been considering, prevented as it is in such cases from obtaining an exit through its natural excretory channels?

CREATINE AND CREATININE.—*Formulæ:* Creatine, $C_8H_9N_3O_4+2$ Aq. —Creatinine, $C_8H_7N_3O_2$.—[1]

Creatine.—This substance, discovered by Chevreul, in 1835, is crystallizable, and is derived from the juice of flesh. It is stated to be "present in the blood and urine of man and of all animals hitherto examined." (Thudichum, *op. cit.*) Both this substance and creatinine, in the form of chloride-of-zinc salt, were found in the urine by Heintz and Pettenkofer, simultaneously, in 1844; but these chemists did not then recognize their identity with the above-mentioned product of the juice of flesh. Liebig, in 1847, demonstrated both creatine and creatinine to be "constant ingredients of the juices of the flesh of nearly all the classes of vertebrate animals, and of the urine of man." (*Idem.*)

Although now a recognized element of the urine, creatine is contained therein in an exceedingly minute proportion. It is always present in the blood, which is a fact important to note in respect to our present inquiry; for, if naturally existing in the vital fluid as a product of a chemical muscular change or waste, it is doubtless innocuous so long as it is finally

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[1] Thudichum.

Chemical Composition of Creatine and Creatinine.

Creatine:	8 equivalents of carbon	48	36.64
	3 " " nitrogen	42	32.06
	9 " " hydrogen	9	6.87
	4 " " oxygen	32	24.43
	Atomic weight of dry creatine	131	100.00

To procure the formula for "crystallized creatine,"

	Take, 1 atom of dry creatine	131	87.92
	and 2 atoms of water	18	12.08
		149	100.00
			Thudichum.
$C_8,N_3,H_9,O_4,+2HO=131+18=149$.			*G. Bird.*
C_8,H_{11},N_3,O_6.			*G. Johnson.*
Creatinine:	8 equivalents of carbon	48	42.48
	7 " " hydrogen	7	6.19
	3 " " nitrogen	42	37.17
	2 " " oxygen	16	14.16
	Atomic weight of creatinine	113	100.00
			Thudichum.
$C_8,N_3,H_7,O_2,=113$.			*G. Bird.*
C_8,H_7,N_3,O_2.			*G. Johnson.*

The formula expresses "crystallized" creatinine.

the excretion of urine, it is not possible that undue accumulation of this substance in the blood should take place. Authors tell us that it is to be considered as undoubtedly excrementitious (Golding Bird, Thudichum); therefore the blood must be depurated from it as it is formed and thrown in upon the circulation, or doubtless the phenomena of systemic disturbance, such as would arise from contaminated blood, would occur. And with this view, we should expect to observe somewhat analogous morbid phenomena to those produced by uræmic poisoning—bearing in mind the close relation to urea which is held by creatine, as has already been mentioned, on the authority of Dr. Thudichum.[2] This supposition, which naturally occurred to us in view of the *excrementitious* nature of the substance in question, seems to find confirmation in the following remarks of the last-named eminent observer. "In disease, the quantity of creatine, together with that of creatinine, might serve to indicate the intensity of any spasmodic or convulsive action. The question as to its quantity in tetanic and epileptic disease is one of high interest. Cases of paralysis agitans, in which the spasmodic action ceases with sleep, may perhaps afford good opportunities for demonstrating the influence of rest and motion; though the different nutrition in the muscle may, perhaps, vary

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[1] "Creatine is present in the blood, by which it makes its way to the kidneys. It occurs in the urine as a regular ingredient, though present in small quantities only. It is partly transformed into creatinine, most probably somewhere between the muscle and the urinary residue out of which the zinc salt crystallizes. For in the muscle, creatine has by far the preponderance over creatinine; in the urine, creatinine over creatine. Creatine is, therefore, truly excrementitious; its relation to urea proves this beyond doubt. Its exclusive occurrence in the muscles shows the seat of its formation; it is, with other matters, a product of the chemical changes in the muscles." (Thudichum, *op. cit.*, p. 120.)

[2] In a uræmic case, Hoppe extracted five times the normal amount of creatine from the muscles of the patient. (Braun, *op. cit.*, p. 99.)

Dr. Golding Bird (*Urinary Deposits*, 1857) has some interesting remarks in reference to the modes of excretion of creatine and creatinine, and also in regard to their relation to urea. "Although we have seen that creatine and creatinine are both found in the urine, we must not conclude that they are entirely excreted in this manner. It is very probable that a considerable proportion of creatine is resolved into uric acid or urea before its final elimination. We have already seen the chemical relation of creatine to uric acid, and to urea; its metamorphosis into the latter body, and into the peculiar substance sarcosin (which requires only the addition of the constituents of water to represent the elements of lactate of ammonia) is so readily effected, that a similar change occurring in the body is rendered very probable." (p. 109, English edition.) We may thus observe that it is very possible for a large amount of creatine and creatinine to be thrown out of the system in other ways than by the kidneys—a fortunate circumstance in renal disease, both when these and other urinary elements are concerned.

the chemical changes in some degree. These suggestions for future researches must not be taken for theories or suppositions." (*Op. cit.*) There are almost no *data*, so far as we are aware, which could enable us to set forth, with any precision, the effects of an undue accumulation of either creatine or creatinine, considered as urinary elements, in the blood. As the author last quoted intimates, "future researches" can alone enable observers to furnish satisfactory details; and although he is careful to repudiate the idea of issuing theories or suppositions, there seems no great presumption in hazarding the latter, as we have done in a former paragraph; especially in view of a dearth of facts which precludes our offering much upon the subject.

It is evident, however, that one practical deduction may be drawn from the fact that these substances are the result of muscular waste, viz., that if there is an excessive amount of them observed in the urine for a long time, this waste will also become extreme—consequently, rest and the appropriate treatment for preventing debilitating action should be observed.[1]

Creatinine.—This "substance is found in the muscles of the vertebrate animals, and in the urine of man in larger quantities than in the muscles. It is the product of the natural or artificial decomposition of creatine * * *." (Thudichum.) Its component elements are carbon, hydrogen, nitrogen, and oxygen.

We have nothing further to present relatively to creatinine than what has already been incorporated under the head of creatine.

HIPPURIC ACID.—(Symbol: $\bar{H}$. Formula: $C_{18}H_8NO_5+HO$.)[2]

Liebig has announced this acid to be a constant ingredient of human urine; a statement which, according to Thudichum, has lately been negatived by Duchek. It is stated that its existence was demonstrated in the urine of young infants by Scheele, Fourcroy, and Reynard. Benzoic acid, when ingested, becomes hippuric acid in the body. (Ure, *Med.-Chir. Transact.*, vol. xxiv.; and Keller, *Ann. d. Chem. und Pharm.*, xliii. p. 198; Thudichum, *op. cit.*)

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[1] See, among other references on this point, Dr. Hassall's work on "The Urine in Health and Disease."

[2] Or, $C_{18}H_9NO_6$.—*Thudichum.*

Chemical Composition of Hippuric Acid.

Carbon	60.335
Hydrogen	4.469
Nitrogen	7.821
Oxygen	22.347
Water	5.028
	100.000

Thudichum.

excess has generally been attributed and easily referable, to peculiarities in the diet. According to Dr. Golding Bird and some others, it seems to be found especially in those who live exclusively upon vegetables, milk, and certain kinds of fruit, and to be most constantly observed in persons of indolent habits. This is esteemed the reason why it is detected in stall-fed cattle, or in well-fed stallions, and not noticed, but replaced by benzoic acid, in cattle that are worked or driven. (*Thudichum et al.*) Dr. Bird ascribes its presence in the urine of nursing infants—a fact already referred to—to their "mal-assimilating the large quantity of carbon contained in the food." This author, moreover, does not consider that it interferes with the production of uric acid; but he observes that in hippuric urine there is generally a deficiency of urea. Reference is also made by him to very interesting cases by Bouchardat, Garrod, and Pettenkofer. In Bouchardat's case, the acid was observed to coexist with albumen in the urine,[1] and an absence of uric acid. The patient had lived for nine years on a milk diet, was fifty-three years old when the case was noted, had resided in the country, had good general health, was in easy circumstances, was the mother of one child, and had ceased to menstruate at the age of forty-five. Gastric and hepatic difficulties of an obscure nature led to her adoption of the milk-diet, and her health was restored. She then partook of a more mixed diet, eating some meat and vegetables; after a time she again became ill, and the chief symptoms were lassitude, dryness of the skin (perspiration having previously been profuse); vague pains in the hepatic region; jaundiced hue; the feces were black; the mouth dry, with a bad taste; there were headache and tinnitus aurium; imperfect vision; palpitation of the heart; excited pulse; anæmic murmur in the carotids; some œdema of the lower limbs; dyspnœa. The chief phenomena, however, were excessive thirst and increase in the quantity of the urine. She often drank from six to ten pints of water in a day. The patient died exhausted.

Dr. Garrod's case was observed in the person of a young man, twenty-three years of age. The first signs of constitutional disturbance were "general malaise," with an excretion of an excess of urea from the kidneys, accompanied by a deposit of the ammoniaco-magnesian phosphate. Atonic dyspepsia, with lumbar pain, succeeded. At this time, hippuric acid, in "long crystals," was detected, and these were slowly incrusted with uric acid. This lasted for several days, and a pint of urine yielded about 40 grains of hippuric acid. Uric acid and urea were observed in normal proportions. The hippuric acid soon decreased, and the urine finally became normal. No information as to the source of the hippuric acid could be obtained from the history of the patient. He had lived on a mixed diet, and never used any excess of vegetable food, nor had he ever taken any benzoic acid." (*Op. cit.*, p. 211.)

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[1] Dr. Prout remarks that both xanthic oxide and hippuric acid "are undoubtedly of albuminous origin." (*Op. cit.*, p. 238.)

The case reported by Dr. Pettenkofer is regarded by Dr. Bird as perhaps the most interesting of the three. The patient was a girl thirteen years old, affected with chorea, and long subject to it, under the care of Dr. De Marcus, of the Julius Hospital, Wurzburg. There had also been "anomalous hysteric symptoms." She had for a long time lived on apples, bread, and water, refusing any other food. The urine was yellow, limpid, and faintly acid when first excreted; it soon became alkaline, and deposited crystals of the triple phosphate of magnesia. Adding hydrochloric acid to it, after moderate concentration there was "a copious formation of crystals of hippuric acid. The addition of nitric acid, by its oxidizing influence, caused the deposit of hippuric to be replaced by one of benzoic acid. In 1000 parts of urine there were—of

"Water	959.332
Solids	40.668
	1000.
Solids soluble in alcohol	18.451
" insoluble in alcohol	9.417
Anhydrous hippuric acid	12.800
	40.668

Fixed salts, containing much carbonate of soda, 19,599.

"The characters of the urine in this case approached those of an herbivorous animal, in the presence of hippuric acid and of carbonate of soda in the ash, as well as in the absence of uric acid.

"The hippuric acid disappeared, and the urine assumed its normal proportions on inducing the girl to return to a mixed diet." (*Op. cit.*, pp. 211, 212.)

We have given the substance of these cases, because they seem to bear so directly upon the portion of our subject now under examination. If, as may reasonably be inferred, the morbid phenomena, both the early and the later, may be ascribed to that state of the system which at last declared itself by the discovery of an excess of hippuric acid in the urine, we may logically argue that this was the morbific agent; and that the surcharging of the blood with it, and the contamination of the various organs by this vitiated current, is the most plausible explanation. At all events, there seems to have been a direct connection between the morbid condition and the excess of the acid in the system. Dr. Bird and others, as has been mentioned, ascribe its presence in the urine in great excess, to the use of a not sufficiently nitrogenized diet, or to mal-assimilation of the carbon of the food. It has been presumed possible that, through the kidneys, hippuric circumstances, the most disastrous results would seem to be unavoidable.

There is no symptom or set of symptoms, so far as we are aware, which would indubitably indicate an excess of hippuric acid in the blood; and the manifestations which we have enumerated, occurring as directly antecedent phenomena to the detection of such an excess, and seemingly dependent upon it, are only to be taken as *probably* the explanation thereof. It is, at least, reasonable to conclude, as we previously remarked, that when the acid appears, more or less suddenly, in excess in the urine, it *has been* equally so in the blood, and for a longer or shorter time—the period, possibly, being indicated more or less distinctly by certain morbid signs. Dr. Golding Bird closes his remarks upon the Pathology of Hippuric Acid in the following terms: "My own experience in these cases has been too limited to justify my offering any opinion on the pathological complications attending them. From what little I have observed, I feel inclined to believe that when an excess of hippuric acid exists, it may always be regarded as traceable to, or pathognomonic of, the deficient function of the liver, lungs, or skin, the great emunctories of carbon; or to the use of food deficient in nitrogen. It hence follows, that our treatment will consist in appealing to the function at fault, and carefully regulating the diet.

"I would suggest the propriety of seeking for the presence of hippuric acid in the urine, where it is copious, of low specific gravity, but slightly acid or neutral, and occurring in persons who have a dry and inactive state of surface, with anæmia. In many pseudo-chlorotic cases in both sexes, I am inclined to believe an abnormal proportion of this acid will often be met with." (*Op. cit.*, p. 213.)

Dr. Thudichum refers to the discovery, by Lehmann, of hippuric acid in diabetic urine, whenever he had sought for it; and also in the acid urine of fever-patients, "of which it is said to cause, in part at least, the acid reaction." Hünefeld and Duchek confirmed the experiments of Lehmann. Schlossberger found hippuric acid in the scales of ichthyosis. Whether this was only an isolated instance, "or whether it is of frequent or constant occurrence in that disease," is not stated. (*Auct. ante cit.*)

Many observations are needed before we can attain to any more precise knowledge of the pathology of hippuric acid. The subject is yet in that undeveloped state which induced Dr. Thudichum to conclude his chapter upon it in these words: "The reader will think this a very unsatisfactory chapter, and so indeed it is. We want observations, for which there is a large field open. But undoubtedly some technical difficulties will have to be overcome first, before the analysis of hippuric acid can be made with sufficient accuracy." (*Op. cit.*, p. 152.) This author has recently investigated the subject in its chemical, physiological, and pathological relations; and if he finds the stores of information in regard to it so meagre, and if

Dr. Prout was obliged to confess that he was not aware that hippuric acid, either in excess or in deficiency, is characteristic of any peculiar disease (*op. cit.*, p. 239), we surely need not shrink from avowing the poverty of our own knowledge in the matter.

CHLORINE : CHLORIDE OF SODIUM.[1]

Were we to follow Dr. Golding Bird's estimate of the "essential" elements of the urinary secretion, we might now pause in our examination of the list of ingredients which we at first enumerated as entering into its composition. Dr. Bird, after mentioning what he terms the "Organic Products," viz., urea, uric acid, creatine, creatinine, colouring and odorous principles, together with hippuric acid and lactic acid, which latter he also styles "accidental constituents," says that this "class of ingredients can alone be considered as really essential to the urine, and characteristic of it as a secretion, the kidneys being the only organs which normally eliminate these elements from the blood." The *saline* ingredients, as he remarks, "are met with in most secretions of the body, with the exception of the sulphates, which are rarely found except in the urine." The "ingredients derived from the urinary passages" (Dr. Bird's *Third Class*) are found "in all fluids passing over mucous surfaces, the phosphate of lime being derived from the mucus, of which it is a constituent."

Since, however, there are many interesting and important points connected with the consideration of the remaining constituents of the urine as given by Dr. Thudichum, whose table we have adopted in preparing this essay, we will bring them separately under consideration according to our original plan. What we have to present, however, will naturally be more general, since we have no affections to consider in this relation, which like gout and rheumatism seem to depend so entirely upon some morbific matter retained in the blood. That an excess or diminution of the chlorides and of other matters in the system, has a greater or less bearing and significance in certain diseases, seems to be proved in many instances, and in others rendered extremely probable. It will be our object in the remainder of this essay to illustrate these positions so far as we may be able; bearing in mind that our main purpose is to indicate the results determined by the undue presence of these elementary substances in the circulation.

With regard to the mere presence of *chloride of sodium*—which substance we shall make the foundation of our remarks—in the blood, it is well known that there is always a greater or less amount taken into the system with the food. There is, indeed, a strong natural appetite for salt, both in men and animals; which, however, varies remarkably in different

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[1] Chemical Composition of Chloride of Sodium:—

$$\textit{Formula:}\ \mathrm{NaCl.}\left\}\begin{array}{l}\text{Sodium . . . 23.3}\\ \text{Chlorine . . 35.5}\end{array}\right\}58.8{=}1\ \text{equiv. chloride of sodium.}$$

ingested in enormous and unnatural quantities; or unless, through other influences, the proper balance of its proportions in the blood be permanently or for a long time disturbed.

The valuable experiments of Barral,[1] Regnault, and Reiset, alluded to by Dr. Bird, Dr. Thudichum, and others, led to the conclusion that the elimination of the nitrogenized elements of the urine was facilitated by the action of the chloride of sodium. Dr. Thudichum thinks that if equally careful experiments were again conducted "by the more accurate methods" now at our command, we should acquire very important information in respect to the "causes and influences" which determine and modify the amount of chlorine thrown off by the kidneys; and this especially if the feces and other *excreta* were taken into the calculation. Barral ascertained by his experiments, both the whole quantity of chlorine taken with the food, and also that of chlorine and urea excreted. The action of chloride of sodium is certainly salutary also in another way; and which is particularly pointed out by Dr. Thudichum, viz., by its causing thirst, and consequently inducing the ingestion of an increased quantity of water, the diuretic influence of which, by producing a more copious urinary flow, "carries away not only the salt, but also organic ingredients in solution." (*Op. cit.*, p. 165.)

The Relation of Chlorine to Pneumonia and other Acute Diseases.—The very striking fact of the rapid diminution, and occasional temporary disappearance of the *chlorides* in the urine of pneumonic patients—first pointed out by Simon and Redtenbacher, and subsequently sedulously tested by several observers, amongst whom Dr. J. H. Bennett may be named as having supplied us with a large amount of clinical observation—naturally arrested the attention of pathological chemists and medical practitioners. It was at first supposed that the above-mentioned diminution was distinctive of the pneumonic inflammation; but subsequent researches seem to preclude this idea. Dr. Thudichum has lately announced the following proposition relative to this point: "The result of many observations of Vogel and others, last, of myself, then, is that *in all acute febrile diseases the amount of chlorine discharged in the urine sinks rapidly to a minimum, say one hundredth part of the quantity normal to the individual, until at last, in certain cases, it disappears entirely for a short time. When the diseased action is abating, the amount of the chlorides rises during convalescence, sometimes above the normal average.*" (*Op. cit.*, pp. 165–6.)

While, therefore, this diminution in and temporary disappearance of the chlorine is not found to be solely characteristic of pneumonia, the cases of that disease in which it has been observed afford very striking illustrations of the fact. For detailed accounts of these, the recent work of Dr. Bennett, already referred to, may be consulted with great advantage. Dr. Beale, of London, has also given us much reliable information upon this important topic. (See *Medico-Chirurgical Transactions*, vol. xxxv.) The rule in pneumonia seems to be that the diminution of the chlorides indicates the progressive stage of the disease; at its height, the chlorides may wholly disappear; their reappearance is a sign of improvement, with cessation of the inflammatory action, and occurrence of the *crepitus redux*. Dr. Bennett thinks it established that, although absence of the chlorides may be found to exist in some other diseases, and may thus lessen the value of the sign in pneumonia, it yet leaves it unaffected in importance, "as pointing out the onward progress of that disease." (*Op. cit.*, p. 640.) The appearance of the chloride of sodium—thus excluded from the urine of pneumonic patients—in the *sputa*, and its desertion of the sputa when it again becomes manifest in the urine, is another remarkable fact connected with these observations. Experiments conducted by Mr. Seymour, Clinical Clerk, upon more than sixty pneumonic patients in Dr. Bennett's wards, established the fact that the chlorides were absent in all but one; and that was a case of phthisis, with *intercurrent* pneumonia.

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[1] Barral, S. A., "*Statique chimique des Animaux, appliquée specialement à la question du sel,*" Paris, 1850. (Thudichum.)

The question to which we now recur, is virtually that at the foundation of our present researches, viz., *does any morbid action result from the retention of the chlorides in the blood?* Irrespective of what we have already said of the avidity with which the chloride of sodium is sought by man and animals, and its innocent nature unless inordinately ingested—when, indeed, it would in all probability be either vomited or discharged from the bowels—we learn from chemical and medical authority that the blood always retains a portion of the chlorides. The fact of the chlorides being found in large quantity in pneumonic sputa, is explained on this ground by Dr. Thudichum, viz., that sputa being, in part at least, "extravasations and exudations from the blood," the chlorides would naturally appear in a substance partly composed of exuded and "stagnant" blood. It does not seem, then, from all that we can discover is as yet known, and considered as material from which to draw conclusions, that pneumonia, or the other diseases in which the absence of the chlorides from the urine is remarked as a feature, can be distinctly ascribed to that fact as a prime cause. Were this to be predicated of any one affection, however, it would certainly be of pneumonia. An extensive field is open for important and interesting observations in the direction of the present inquiry; but should it be hereafter ascertained that the amounts of chlorine absent from the urine, and therefore presumed to be circulating in the blood, are to be considered as more or less poisonous, either by their quantity or quality, we still must remember, in estimating such an action, that there are other channels of stant occurrence of diminution or abolition of the chlorides in pneumonia, is a curious and important fact; but, as yet, not sufficiently illustrated by observations and study, to take the place of an etiological element of disease. Dr. Thudichum states, in respect to the questions under consideration, "the absence of the chlorides in the urine does not necessarily involve the absence of chlorine from exudations. For the latter are products of diseased action derived directly from stagnant blood, and certainly not subject to the specific laws of secretion. The presence of chlorine in sputa, therefore, at a time when it is absent from the urine, is not sufficient proof of a determination of the chloride towards the inflamed lung; a proposition which, moreover, loses all probability from the partial or total disappearance from the urine of the chloride in all acute diseases." (*Op. cit.*, p. 166.) He then enumerates bronchitis, typhus, acute rheumatism, pyæmia, and pleuritis, as examples of this fact; and also refers to the influence exerted in the system by varying quantities of chlorine introduced into it with the food, ascribing no inconsiderable amount of this effect to the sort of diet used by the patient when the quantity of chlorine in "pathological urine" is to be estimated. In most acute diseases, it is known that patients take but little food—often none—and that the articles they eat are often unsalted. Another fact of consequence, which is insisted on by Dr. Thudichum, is, "that urine containing no appreciable trace of chlorine is secreted from blood containing a certain amount of it; from which it follows that the composition of the blood is such as not to allow any further removal of chlorine, or that the kidneys have lost their secretory activity as regards chlorine, as well as (which has been seen to be the case) with reference to water." (p. 167.)

As has been shown to be the fact with regard to pneumonia, so it may, in the opinion of the latter writer and others (and it is no less deducible analogically), be considered available to esteem the amount of chlorine in the urine, a gauge of the amount of morbid action going on in the system in certain other affections. That is, an estimate, more or less accurate, may be made as to the *severity* and *activity* of the disease. The minimum of chlorine in the urine, in making such estimates, Dr. Thudichum places at 0.5 gramme; and after that, in the intensity of the disorder it may, as we have seen, be altogether wanting. "This may be the combined effect of an entire loss of appetite, copious serous diarrhœa, or other serous exudations; of secretions, such as perspirations; and of the want of secreting power of the kidneys. A rise in the amount of chlorine, on the other hand, indicates a steady abatement of the acuteness of the disease, and is a good measure of the returning appetite and improved digestive powers of the patient."

We referred, previously, to the experiments of Barral and others, which seemed to show increased activity of nitrogenous elimination through the acid to the stomach, and soda to the bile, also exerts an important physiological influence in aiding the metamorphosis of tissue, and consequent depuration of the blood." (*Op. cit.*, p. 127.) If we accept this as true, we not only need not ascribe any morbid effects to the retention of chlorine —or of chloride of sodium—in the blood, but rather deem its presence desirable and salutary—at all events, in the vast majority of cases.

Certain of Hegar's conclusions, which were arrived at under the superintendence of Liebig and Vogel (G. Bird), are interesting in this connection. We select a few, in illustration :—

> "The amount [of chlorine in the urine] varied in different individuals, depending partly on the food, and partly on habit of life and constitution." "It was increased by exercise and copious draughts of water, which appeared to act by washing it out of the system, as the augmentation was only temporary." "Indisposition diminished the quantity." "In health, though no chlorides were taken with the food, they were always found, and must therefore have been obtained from the blood or tissues." "When a larger quantity was taken than usual, the whole did not escape from the system by the kidneys, nor even the bowels."

The latter two facts would seem to go far to prove the innocuousness of even considerable amounts of chlorine in the blood. Dr. Day (*Contributions to Urology*) is quoted by Dr. Bird as testifying to the fact to which we have previously called attention ; that the chlorides are diminished in all cases of disease accompanied by copious exudation from the blood.

We notice that Dr. Bird asserts, as from Dr. Beale, that the nature of the diet necessarily adopted in pneumonia and other acute diseases, seems insufficient to explain the absence of the chlorides from the urine. Doubtless this default of ingestion of chlorine will not fully meet the requirements of the case in the way of explanation, but it seems only reasonable to allow it no inconsiderable weight. The following are Dr. Beale's very important propositions :—

> "1. That chloride of sodium is totally absent from the urine of pneumonic patients at the period of complete hepatization of the lung.
>
> "2. The chloride reappears after the resolution of the inflammation.
>
> "3. The chloride exists in the blood in the largest quantity, when most abundant in the urine, and *vice versâ*. [We may here, again, find reason for inferring the harmlessness of even large quantities of chloride of sodium in the blood; for when it is considered that under these circumstances, *were it easily, or at all, a cause of disease*, the conditions for the development of morbid action abundantly exist, we certainly have sufficient ground for the above opinion.]
>
> "4. The chloride exists in very large quantity in the sputa of pneumonic patients.
>
> "5. There is reason to believe that in pneumonia the chloride is determined

the inflammation."

The validity of this latter proposition, as we have previously stated, is denied by Dr. Thudichum; and if it is meant thereby, as it would seem to imply, that the chloride of sodium is the morbific material, we cannot see any sufficient reason to suppose such a relation of cause and effect as by any means certain. That there is a degree of plausibility about it, we confess; but not, at present, any satisfactory proof.

In chronic diseases, the amount of chlorine excreted is usually diminished. This would tend to ratify the supposition that failure of the appetite, and the consequent less ingestion of food, explain the decrease in the chlorine introduced into the system; and the fact consorts, also, with the enfeebled nutrition. Lecanu found the quantity of chloride of sodium very small in the urine of women and old men (*Simon's Chemistry*, vol. ii. p. 167. Sydenham Society's edition.) Observers point out *diabetes insipidus* as an exception to this rule; the chlorine discharged being in excess. So, in dropsy, Vogel found the chlorine increased under artificial diuresis. Chlorine here becomes a gauge of the powers of digestion. It may be inferred that digestion is in good order, when from six to ten grammes are excreted in twenty-four hours; any quantity below five grammes, for the same period, declares an impaired nutrition, unless the diminution can justly be ascribed to a diet very deficient in chlorine, or entirely without any. So those discharges which diminish the amount of chlorine contained in the blood, "as serous diarrhœa, exudations and perspirations," should be taken into account in making an estimate of the morbid action. When the amount of chlorine is very largely increased, and there has been no corresponding plentiful supply by ingestion, *diabetes insipidus* may be inferred. "In dropsical and hydræmic conditions, an increase of the amount of chlorine is a favourable symptom." (Vogel, by Thudichum, *op. cit.*, p. 168.)

If this portion of our subject seems to have been presented in a somewhat negative manner, it is because the information attainable in reference to it is of the same nature. We seem able to say rather wherein the presence of chlorine in the blood—at all events of such amounts as are derivable from diverted excretion thereof by the kidneys—is harmless or even beneficial. Notwithstanding, it must be confessed, that observations and researches upon this point are not available in such quantity as to enable any one, at present, to set forth entirely reliable practical rules and conclusions.

SULPHURIC ACID. (Formula: SO_3+HO[1]: Equivalent, 16.0 Sulphur; 24.0 Oxygen=40.0, Sulphuric Acid.)

A variable, and often very considerable amount of sulphuric acid is discharged from the body by the kidneys during each twenty-four hours. When it is considered that sulphur must nearly always exist in the blood, in greater or less amount—being derived from the food—it will be conceded that it is unlikely that any retention of it therein, even after its oxidation, unless it be present in very large and improbable quantities, would be influential in inducing actual disease. We will examine the known relations of sulphuric acid, as contained in the urine, to the system—so far as facts enable us to present anything worthy of credence and likely to prove of service.

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[1] "Being the hydrate of sulphuric acid." (Thudichum, *op. cit.*)

Liebig, referring to Wöhler's experiments, ascribes the sulphuric acid generated in the system, to the action of the oxygen of the atmosphere upon the sulphur introduced into the blood through the medium of food—and this is particularly true of the albuminous portion thereof, which, of course, constitutes, as a general thing, a large amount of the whole. This process of oxidation, and consequent manufacture of sulphuric acid in the system, carried on as it is through the medium of the blood itself, seems to confirm our previously announced opinion, that this acid, in itself, is innocuous. If a very large amount were long and habitually retained in the circulation, it will be easy to understand that mischief might ensue. Before examining any possible or probable pathological issues, we will further allude to certain physiological facts connected with the existence of sulphuric acid in the system, and its excretion from it. It should be said, before proceeding further, that the oxidizing process above mentioned accounts for the surplus of sulphuric acid which is eliminated from the body, over and above what is ingested with the food, in the form of sulphates. (Liebig, Simon, Thudichum.) It is therefore evident that a full animal diet will, by introducing more sulphur into the blood, increase the amount of sulphuric acid in the urine—and that, under the same conditions, more must, for a time at least, be contained in the blood. The experiments of Lehmann on himself show conclusively the effect of different sorts of diet in increasing or diminishing the quantity of sulphuric acid passed in the urine. Thus, while on a "mixed" diet, 7.026 grammes of the acid were collected during twenty-four hours; when animal food was exclusively used, the quantity rose to 10.399 grammes in the same time; when living on vegetables exclusively, only 5.846 grammes were obtainable in the course of one day. Dr. Thudichum, commenting upon these quantities, pronounces them very high, and is inclined to attribute this to Lehmann's appetite. He was, it is true, in fine health and of robust constitution, and therefore some allowance is to be made; but, as Dr. Thudichum also implies, the intrinsic value of the experiments is unaltered by the mere amounts. The *ratio* of formation of the acid, under the differing influences, is the essential point. Certain very conclusive experiments by Vogel, Clare, and others upon this subject, are given in some detail in the work of Dr. Thudichum. The results are the same in character as those obtained by Lehmann.

quired by the system in its different states. We know the beneficial effects derived from its medicinal use as a tonic, refrigerant and astringent; and thus it would appear that in certain states of the constitution it is especially suitable—we may, indeed, say indicated. Whether a certain amount of the sulphates must enter into the circulation in order to perfect secretion, "or whether sulphates may be retained and accumulated in the economy," is, at present, unknown. Dr. Thudichum, while stating this fact, mentions that neither rest, nor activity, nor the ingestion of large quantities of water, seemed materially to affect the amounts of sulphuric acid in the urine, in certain of the experiments of Clare and Gruner. Vogel, however, he states, believed "it probable that such influences exist, that the secretory activity for sulphuric acid is dependent upon certain individual and cosmic influences" (*op. cit.*, p. 175); and this is rendered nearly certain by the fact of the difference in the rapidity of oxidation of the introduced sulphur observed in various persons. A very significant opinion of Vogel, quoted by Dr. Thudichum, is of importance as affording a valuable suggestion closely connected with our present inquiries, and in respect to which we need more extended observation. It will be seen, as we just remarked, that the suggestion bears directly upon the point which now engages our attention; and all inquiries of this nature must tend greatly to advance our knowledge of any diseased conditions (and of the remedial measures suited to them) which may reasonably be supposed to depend, even remotely, upon an undue accumulation of the products we are considering, in the blood. The statement to which we have reference is as follows:—

> "Vogel, also, from observation, is of opinion that the prolonged use of sulphates in digestive doses is decidedly weakening, and believes it probable that this depressing action may be due to an accumulation of the salts in the system. When to this it is added that sulphate of soda in larger doses is an emetic, and sulphate of potash a poison, the question as to the influence of sulphuric acid and sulphates in the urine becomes one of sufficient importance to fix the attention of future inquirers." (*Loc. cit.*, p. 176.)

From the same sources of authority we learn that the amount of sulphuric acid in the urine is diminished in febrile diseases. This, as is plausibly suggested, may, in great measure, be ascribable to the nature of the food taken, viz., mainly vegetable—less sulphur being thus supplied to the blood; and it must also be remembered that the *quantity* of food is very greatly diminished under such disordered conditions.

Dr. H. Bence Jones (*Medico-Chirurgical Transactions*, vol. xxxiv.) found the amount of the sulphates increased in *chorea*, and in aggravated cases of *delirium tremens;* and he likewise notes a similar augmentation, both of the sulphates and phosphates, in cerebral inflammation. He ascribes this occurrence to the rapid disintegration of muscular tissue in the former affections, and to excessive and rapid oxidation of the cerebral substance in the latter.

Vogel found, in three pneumonic patients, the amount of sulphuric acid discharged, exceptionally, "above the normal average." In chronic diseases, while the quantity was variable, it was generally below the standard amount. It was not increased under a diuretic action which largely augmented the discharge of the chlorides, as in cases of dropsy. The ingestion of sulphuric acid and sulphates by patients labouring under chronic disease, alone produced any increase in the amount excreted; and a hearty meal of animal food had the same effect in patients suffering from diabetes.

While we are obliged to speak doubtfully as to any abnormal effects ascribable to the action of various amounts of sulphuric acid retained in the circulation, we can say—as we have already once stated—that such effects, from any increased amount likely to be thrown into the blood by failure of the renal excretory function devoted to separating this acid, are not such as to be defined, with our present knowledge; nor can we believe any very serious results likely to follow under such circumstances. If *all* the urinary elements were retained, or only such as greatly predominate—and which we have previously considered—then the other accidents, already detailed, would very surely mask any minor morbid action; and if either urea or uric acid predominated, we should have their peculiar concomitant or resulting phenomena, to the exclusion of any weaker manifestations. While, therefore, nothing positive can be charged to the presence of sulphuric acid in excess (more or less) in the system, we are fortunate in having suggestions from reliable sources, and accurate chemical observations from many competent hands. And all will join Dr. Thudichum in estimating very highly the determination of the quantity of this acid in the urine as being a sort of index of "the amount of disintegration of albuminous matters in the system, in cases where the ingestion of sulphur in any form or combination is very low or altogether suspended." He goes on, also, to remark that possibly a degree of correspondence of the acid with urea, in amount, might be found to exist, "supposing their inclination to pass the kidneys to be equally great. But upon this point there are yet doubts." (p. 177.) If both sulphuric acid and urea be largely excreted, we are to infer that very free oxidation is going on in the system, and is due to the ingestion of animal food in abundance. The opposite condition with respect to sulphuric acid, would go to show a diminution in, or entire deprivation of animal and vegetable food. These states may be either constant or accidental. (Thudichum.) We have already hinted that a sudden, temporary increase in the amount of sulphuric acid excreted, would seem to indicate a reception of sulphur, in some of its forms, into the system, and that too in large quantity.

Dr. Thudichum thinks that new analyses of the blood will have to be made, and without incinerating it. This, he states, "destroys the relative hope not only for more accurate chemical information upon these points, but also that new and more abundant pathological inferences will be drawn from such researches. The fact that the production of sulphuric acid is proved, to all appearance, to be restricted to the blood, and that it is formed through the agency of the oxygen of the air, by means of the respiratory function, is highly important in relation to the present portion of our subject. Its being formed, in great measure, in the blood, is favourable to the idea we have before mentioned, viz., that the vital fluid will be more likely to tolerate its presence, even in large quantities. If this opinion should be deemed merely speculative, we can only say that most of the information now existing upon the subject is of the same nature.

Another interesting question, founded upon the seeming fact that the sulphuric acid is in great part formed in the blood, from the aliments—and also referring to the remark by Liebig, "that the acid nature of the urine of carnivorous animals, as well as that of men, depends upon the nature of the bases partaken of in the aliments, and upon the particular form of their combination"[1]—is, how far the office of the kidneys is to finish the "final oxidation, or that stage of disintegration of albuminous matter in which sulphur, in the form of sulphuric acid, leaves the organic combination, joins a base, and appears in the urine." (Thudichum, *op. cit.*, p. 178.) These, and other chemico-pathological inquiries, as has already been intimated, must be left to future investigators to determine. So far as our present means afford us any ground for the pathological inferences connected with this portion of our subject, we are compelled—after having presented what, for the greater part, is as yet conjectural and undetermined, although seemingly interspersed with the elements of truth, and certainly accompanied by many precise chemical facts—to rest the matter here.

PHOSPHORIC ACID.—(Formula: PO_5+3HO.)[2]

This acid is the next regular constituent of the urine which we are to consider, pathologically. Previous to entering into any particulars, it may

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[1] Liebig, quoted in Simon's Chemistry, vol. ii. p. 153. (Lancet, 1844.)

[2] "The common or tribasic phosphoric acid."

Chemical Composition of Phosphoric Acid.

1 equivalent phosphorus	P=31.436
8 equivalents oxygen	=64.000
3 equivalents hydrogen	= 3.000
1 equivalent of phosphoric acid	=98.436

"The theory which assumes P to be a double atom, and the single atomic weight=15.718, uses P_2 as the symbol for the above equivalent of phosphorus. This is an explanation to the reader, should he find himself embarrassed by the formulæ of different authors."—*Thudichum.*

fore treat of it in much the same manner as was adopted in examining the latter substance.

Phosphorus enters the system constantly, and often in very considerable quantities. It is taken with the food, and it has also been long medicinally ordered. Within a short time, indeed, the *phosphates* and *phosphites* of lime and soda have been prescribed with variable results, as *nervines*, and also as being suited to combat the ravages of tuberculous disease of the lungs. In certain cases, we may add, they are reported to have been of service; and we can recall cases of general prostration, and of what has been sometimes termed "nervous debility," in which we have used them with apparently marked benefit. To Dr. Churchill, now of Paris, belongs, we believe, the credit of suggesting their persevering employment in threatened, or actually existing, pulmonary consumption. The success attained, although flattering in many instances—as we learned, personally, not long since, in the French capital—has not, by any means, justified the expectations at first excited.

This seeming digression from the immediate course of our subject, is not, after all, an element actually foreign to its consideration; for we may thus at least be led to examine what cases will be likely to derive benefit from the ingestion of phosphorus into the system.

The amount of phosphoric acid present, normally, in the urine, is considerably less, according to Becquerel and Rodier, Golding Bird, Johnson, Prout and others, than that of sulphuric acid; and it is found in combination with lime, ammonia, soda, or magnesia. Dr. Thudichum, we notice, in his estimate in the table from which we have taken our list of urinary constituents, has made the amount greater. In the system generally, the quantities existing at different times, will vary from nearly the same causes as have been assigned for the changes in the quantity of sulphuric acid; viz., the nature and amount of the food taken, and the ingestion or otherwise, of phosphorus in a medicinal form. The same difference in rapidity of excretion of phosphoric acid, is observed in different persons, as is true with regard to sulphuric acid. And in respect to the activity and amount of excretion, the same variations are to be remarked as have been recorded for chlorine and sulphuric acid. Therefore, renal disease must be considered an important *pathological* influence in respect to the amounts excreted, as personal peculiarities and fortuitous circumstances as to diet, &c., are observed to be, *physiologically*. We learn from Vogel, that copious draughts of water will increase the amount of phosphoric acid excreted by the kidneys—a fact similar to what has been mentioned in respect to the chlorides. As Dr. Thudichum remarks, in commenting upon this point, and as we have previously intimated, "the organism may at one time contain an excess of phosphoric acid, at other times the acid may be deficient."

until the normal amount of phosphoric acid contained in all parts of the body, and its changes and variations, within the range of perfect health, be known. And then the examinations will have to comprise a complete analysis of all food, and of all excretions." (*Op. cit.*, p. 188.)

The decrease of phosphoric acid in acute disease, noticed by Vogel, is ascribed partially, as was the fact with regard to sulphuric acid, to the *diminution* and *quality* of the diet ordered or made necessary. When the rations are richer and more liberal, the phosphoric acid increases in quantity; and in convalescence the normal amount is often exceeded, owing to the increased ingestion of food. The decrease of phosphoric acid bears a notable proportion to the *period of time* the illness lasts—even if the attack be violent, and much fever accompany. If short, there is little variation in the amount of acid excreted, and *vice versâ*. Severity and prolongation of the disease, with great diminution of, or total abstinence from food, causes very marked decrease in the quantity of phosphoric acid appearing in the urine. In *chronic diseases*, no rule is observed. Sometimes, and indeed usually, there is great diminution in the amount, and again there may be excess.

Certain statistics supplied by Dr. Thudichum, relatively to the quantities of phosphoric acid excreted in various diseases, and at different stages of each affection, have an important bearing upon the subject. In a table given by him (*op. cit.*, p. 191), the most remarkable points, perhaps, are that the largest amount mentioned ("maximum") as excreted, was in the case of a *female* with diabetes insipidus (7.8 grammes); the next largest, in a *male*, suffering from *hydruria* (5.8 grammes). This seemingly ratifies the remarks and observations previously made, that where the kidneys are most actively employed, the most phosphoric acid is excreted.

If the question be now asked, whether there is any relation between the deficient excretion of the acid in question, and the diseases which have been specified as exhibiting less of the excreted product during their acute course—this implying the retention of a greater or less amount of the substance in the blood—we must admit that no positive proof of this absolute connection as yet exists. In this respect, as in many others pathologically important, the subject is very much in the position of the one last examined. We have already, incidentally, referred to the detection of an increased amount of the phosphates—in connection with the sulphates—in the urine of persons with cerebritis, by Dr. H. Bence Jones. This phenomenon, ascribed by that accomplished observer to rapid oxidation of the cerebral tissues, will, we conclude, hardly justify us in ascribing the inflammatory attack upon the brain, in any degree, to increase and undue retention of the phosphoric acid in the circulation. It does not appear, moreover, that the kidneys were at all disabled; had they been, it is not impossible but more serious mischief might have occurred in such cases—although it is the bowels, as well as from the kidneys.

EARTHY PHOSPHATES.[1]

We have previously mentioned the medicinal use of the phosphates, with the purpose of adding to the nervous force, and in the hope of obviating tuberculous disease. The phosphates of lime and of soda have thus far been prominent in these respects. The latter is physiologically essential to the integrity of the blood and body.[2] (Liebig, Thudichum.) The proportion of earthy phosphates discharged daily is found to be very variable in different persons; and, according to the most reliable authorities, no average amount can yet be declared. Lehmann, when living upon a mixed diet, discharged, on the average, 1.09 grammes, daily; when his food was exclusively of an animal nature, the amount became 3.56.[3]

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[1] *Chemical Composition of the Phosphates.*

Ammonio-phosphate of soda$=PO_5+NaO+NH_4O+HO+8HO$. Acid " " " $=PO_5+NaO+2HO$.	*Phosphates of Alkalies.*
Ammonio-phosphate of magnesia$=PO_5+2MgO+NH_4O+12HO$.	*Phosphates of the Alkalies and Earths.*
Phosphate of lime (acid),$=PO_5+2CaO+HO$. Phosphate of magnesia, $=PO_5+2MgO+HO$.	*Phosphates of the Alkaline Earths.*

Thudichum.

Phosphate of soda	$(HO,2NaO,P_2O_5)+24HO$.
Ammonio-phosphate of soda	$(HO,NH_4O,NaO,P_2O_5)+8HO$.
Phosphate of lime	$(HO,2CaO,P_2O_5)$
Ammonio-phosphate of magnesia . .	$(NH_4O,2MgO,P_2O_5)+12HO$.
Neutral phosphate of soda	$(HO,2NaO,P_2O_5)+26HO$.
Acid phosphate of soda	$(12HO,NaO,P_2O_5)+2HO.)$

G. Bird.

Robin and Verdeil have pronounced the two salts, last described, to be normal constituents of the urine.

[2] "There is no known salt the chemical characters of which approach more closely to those of the serum of blood than the phosphate of soda; there is none more fitted for the absorption and entire removal from the organism of carbonic acid."—Liebig, Researches on the Chemistry of Food, and the Motion of the Juices in the Animal Body. Dr. Gregory's Translation, American edition, by Prof. E. N. Horsford, 1848.

[3] In connection with the presence of phosphoric acid and of chloride of sodium in the system, the following remarks of Liebig have an interest and importance: "In some pathological conditions there has been observed (Schmidt, *Annalen der Chimie und Pharmacie*, vol. lxi. p. 329), at points where bones and muscles meet, an accumulation of free lactic and phosphoric acid, which has never been perceived at those points in the normal state. The solution and removal of the phosphate of

earthy phosphates in the system, would depend very much upon the integrity of the kidneys. If the latter were disabled, and even if not particularly disorganized—sometimes, even, if nearly healthy—there might be large deposition of these substances in various parts of the urinary passages. The circulation would in this manner be freed from an embarrassing amount of them, but the morbid effects of such an abundant deposit would certainly prove very troublesome. Vesical calculi are rarely *entirely* composed of the phosphates. Such is their friable nature and tendency to a pulverulent condition, that they prefer a nucleus of some sort, around which to accrete, rather than to form pure aggregations of their own substance.

Dr. Thudichum believes that "the originators of the term phosphatic diathesis and phosphuria, and their followers, linked a series of the most varied disorders together under this term, which had nothing in common but one symptom, namely, alkaline urine." (*Op. cit.*, p. 211.) He then proceeds to explain in a very clear manner, the reasons for a greater or less acidity or alkalinity of the urine. And alkalinity may thus be often due to a lack of animal food, by which a suitable amount of acid is usually supplied. Therefore the invalid and the poor man are alike liable to pass very alkaline urine—the dyspeptic from want of appetite, and the pauper from want of means. A vegetable or fruit diet, alone, will make the urine alkaline; and those who cannot digest, or imagine they cannot digest meat, and therefore try a vegetable diet, will almost certainly have alkaline urine. In anæmia, a meat-diet will soon produce an acid urine, with the phosphates, where no acidity existed before.

It would appear, then, so far as conclusions can at present be drawn, that a certain amount of phosphoric acid is not only physiologically necessary (*phosphate of soda*), but that certain states of the system require additional amounts medicinally, or by food. The ammoniacal urine of patients who labour under spinal disease or injury, or who are suffering from other affections giving rise to retention and stagnation of the urine, and its alkaline change, is referable to a local cause; and the mischief which undoubtedly results to the circulation by reason of this state of things, is

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lime, and therefore the disappearance of the bones, is a consequence of this state. It is not improbable that the cause, or one of the causes of this separation of acid from the substance of the muscles is this—that the vessels which contain the fluid of the muscles have undergone a change whereby they lose the property of retaining within them the acid fluid they contain.

"The constant occurrence of chloride of sodium and phosphate of soda in the blood, and that of phosphate of potash and chloride of potassium in the juice of flesh, justify the assumption that both facts are altogether indispensable for the processes carried on in the blood and in the fluid of the muscles." (*Op. sup. cit.*, p. 90.)

part and parcel of the causative disease. If inordinate quantities of the phosphates are passed for a long time, we should certainly look for systemic disorder; and doubtless the general health would soon be found to deteriorate. Some *specific* cause might be detected for such failure—unless an unusual quantity of phosphoric acid were being introduced into the system, to account both for the large corresponding excretion, and for unimpaired health—should the latter be observed to exist. But usually, with such a state of things, impaired nervous energy, dyspepsia with irritability, and various functional disturbances, will be present.

The extraordinary case reported by Dr. Golding Bird, of the man who passed very large quantities of the phosphate of lime, without apparent harm to his constitution (excepting that he was always dyspeptic), is believed by Dr. Thudichum to be an instance of imposture. There certainly seems to be some reason for so regarding it. The patient had been under the care "of half the hospital physicians and surgeons in London," during fifty years. It is remarked that very possibly he might wish to be an object of permanent interest to whatever physician attended him, and that he liked hospital quarters. At one time he brought more than an ounce of the above-mentioned salt to Dr. Bird, and which he asserted was passed from himself. His urine was milky, and abundantly deposited the salt, as stated. It is not, however, impossible that he may have been even a longer time collecting the large quantity shown to Dr. Bird, than is suggested by Dr. Thudichum, viz., sixteen days. The man's health was so good that no treatment seemed justifiable, except on account of an apprehension that a vesical calculus might form.[1] Dr. Thudichum does not think Dr. Bird's explanation of the case founded on fact;[2] and he refers to Dr. Prout's remarks upon this point, as follows:—

> "If the reader should not share our doubts, he may adopt the explanation by Dr. G. Bird, for which, however, there is no basis in fact; or he may explain it upon the ground of the following observation recorded by Dr. Prout. (p. 323, note.) This physician examined the body of a gentleman who, during the greater part of his life, had suffered from renal disease, remarkable for being

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[1] It would therefore seem that his *dyspeptic* symptoms were not very urgent.

[2] The following are Dr. Bird's explanatory remarks: "In cases of this kind it is very possible that the phosphate of lime is secreted from the mucous membrane of the bladder, and not derived from the urine. All mucous secretions contain phosphoric acid, combined with earthy bases; and hence if an excess of the latter is secreted with the vesical mucus, it may be washed away with the urine and form a deposit. This is by no means unfrequent in the irritable bladder, depending on the existence of prostatic diseases, &c.: we have a perfect analogy to this in the calculous concretions found in the ducts of glands furnishing mucous secretions. These are all prone to secrete phosphates in too great an excess to be washed away with the secretion; they are therefore retained and form a calculus. These, from whatever part of the body they are obtained, present nearly the same composition." (*Urinary Deposits.* Dr. Birkett's edition, 1857, p. 306.)

attended by the secretion of large quantities of the earthy phosphates. Both kidneys were not only extensively disorganized, but most of the natural cavities, as well as many cysts, were found distended with numerous earthy concretions, of various sizes and composition. The concretions found in those cavities *to which the urine had access*, consisted of the phosphate and carbonate of lime, and more or less of the triple phosphate of ammonia and magnesia, while those cavities or cysts distinct from the renal structure, and to which, therefore, *the urine had no access*, consisted of the calcareous phosphate and carbonate only, without any admixture of the triple phosphate." (*Op. cit.*, p. 213.)

When what is termed the "phosphatic diathesis" exists, or when we find copious phosphatic deposits in the urine, we are to expect in such patients a state of debility, listlessness and exhaustion, mental and physical —a sort of cachexia, with disturbed digestion, and an irritable state of the digestive organs; and also, either some manifest or concealed disorder of the nervous system. To this condition we have already referred. Such symptoms should lead to the adoption of an alterative and tonic treatment, and to such examination of the patient hygienically and constitutionally, as will doubtless soon afford a knowledge of the chief source of difficulty —whether functional or systemic; and if the latter, whether the cerebro-spinal, or renal organs are at fault; or whether the blood itself be surcharged with matters fit only for elimination. Old people often exhibit a train of symptoms indicating troubles referable to what is styled "the phosphatic diathesis." Dr. Bird well describes the state when he writes that there "is irritability with depression, a kind of erethism of the nervous system, if the expression be permitted, like that observed after considerable losses of blood."

It seems peculiarly appropriate to introduce in this place the conclusions of Dr. H. Bence Jones in reference to the pathological bearing of phosphatic salts in the economy—much of what we have previously said seems to find ratification in these opinions, and perhaps we could not better conclude our examination of this department of our subject than by presenting them.

"1. No determination of an excessive secretion of phosphoric acid can be afforded by the deposit of earthy salts, unless the quantity of lime and magnesia in the food be taken into account.

"2. No *real increase* of phosphatic salts occurs in spinal diseases, notwithstanding the existence of deposits.

"3. In fever, and in most acute inflammations, the phosphatic salts are not increased.

"4. In old cases of mania, melancholy, paralysis of the insane, or in chronic cases of disease in which nervous tissues are uninfluenced, no conclusions can be drawn.

"5. In fractures of the skull the phosphatic salts increase only when any inflammatory action occurs in the brain, and in acute phrenitis an excessive increase takes place.

they are introduced with the ingesta; an excess is, however, met with in some functional affections of the brain."[1]

In this connection, we cannot but allude to the zealous, and, as it would seem, very sensible, recommendation, by Dr. Bird, of what he appropriately terms "renal depurants." Knowing, as we do, from unmistakable symptoms, that a poisonous substance is traversing the blood, and thus pervading all the bodily tissues, it is our manifest duty to use some such means for stimulating a sluggish, or even a partially diseased kidney, to freer elimination. And there are many substances which may be effectually employed in this manner, and innocuously, or even beneficially to the kidneys themselves. Indeed, when there is even some degree of risk in demanding extra work from those organs, it is better to tax them rather severely, than to allow the accumulation of morbid matters, of any kind, in the blood. "The alkalies, their carbonates, and their salts, with such acids as in the animal economy are capable of being converted into carbonic acid, including the acetates, tartrates, citrates of soda and potass," are properly "renal depurants." (Bird, *Op. cit.*, p. 452.)

AMMONIA.—Symbol: NH_3; Equivalent, 17.0.[2]

Ammonia exists in comparatively very small proportions in fresh and healthy urine.[3] Liebig, indeed, doubts whether it can indubitably be pronounced an invariable and constant constituent of normal urine. In these doubts he is joined by Lehmann and Scherer. Dr. Thudichum, who has investigated the subject in his treatise already largely referred to, thinks the researches of Boussingault more satisfactory than those of Bœcker and De Vry; and that they tend to show the presence of this substance in the urine. Neubauer (*Journal für Practische Chemie*, Bd. 64, p. 177, and *Anleitung*, § 56), according to the same writer, has afforded the best proof, thus far, of the presence of certain amounts of ammonia in the

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[1] We transcribe these statements as given in Dr. Bird's volume; consulting at the same time Dr. Jones's papers on the Sulphates and Phosphates, contained in the 30th and 34th volumes of the Medico-Chirurgical Society's Transactions.

[2] *Chemical Composition of Ammonia.*

$H_3 = 3.0$	17.65
$N = 14.0$	82.35
17.0	100.00

Thudichum.

[3] Ammonia "is the only volatile alkali with which chemistry is acquainted; and of this property we avail ourselves for its analysis."

"*Demonstration of the presence of Ammonia in Urine.*—The ammonia, which has been liberated from urine by means of milk of lime, is made to pass in the form of gas into a solution of sulphate of silver and arsenious acid; the precipitate ensuing is evidence of its presence." (*Thudichum.*)

this method, which I have already advanced; the ammonia is set free by the addition to the urine of milk of lime. Now, if it can be proved that milk of lime, at the ordinary temperature of the air does not within a reasonable limit of time create ammonia from urea and the other organic substances, we are bound to say that an essential progress would be effected by these researches of Neubauer. The subject of ammonia in connection with the animal economy would be of immense importance, if it should be proved beyond the shadow of a doubt, what Dr. Richardson (Astley Cooper, Prize Essay for 1856, On the Cause of the Coagulation of the Blood) has endeavoured to show, namely, that ammonia is a regular constituent of the blood, and the solvent of fibrin in the living body." (pp. 219, 220.)

According to the same author—who again refers to Neubauer's analyses for the proof of the assertion—"*The ammonia of the salts of ammonia, when the latter are taken into the stomach, passes unchanged through the system and is discharged in the urine.*" (p. 223.)

We have cited the above facts—principally of a chemical and physiological nature—because they are not only interesting, but also have an important relation to the pathological question which presents itself in regard to ammonia considered as a constituent of the urine; and whether its retention in the blood produces any morbid effects. We have not very much to offer upon this portion of the subject; but there are some considerations which are significant. There is a great deal to be learned in regard to the matter—to say nothing of the points in dispute—and principally in reference to the production of uræmia through the agency of *carbonate of ammonia*, as a product of fermentation in the blood. Upon this latter question we have already entered into extensive detail, and have endeavoured to present the actual *status* of the subject, as viewed by many celebrated and industrious observers. We refer the reader to the portion of this essay devoted to *Uræmia;* and will merely add, that all who have examined the facts and theories advanced by Frerichs and others relative to uræmic poisoning, acknowledge the importance of the investigations, and also seem fully aware of the conspicuous position which ammonia would assume as a morbid agent in the human system, if it should ever be proved to possess such a toxic influence as some now accord to it. Dr. Thudichum remarks upon this point: "If what some have ventured to bring forward as a defined feature of certain forms of disease of the kidney can really be maintained, namely, that the urea retained in the blood may there undergo decomposition into carbonate of ammonia, and give rise to the symptoms described as uræmia, the pathological indications of ammonia in the urine would be all-important in those diseases. And though quantities of ammonia might be excreted by the lungs, skin, and bowels, yet the ble. However probable such a process, under given circumstances, may be, actual and direct proof would be required to make it a fact; and this we cannot say to have been afforded by the originators of the theory. We know, on the contrary, that the test said to be diagnostic of the presence of ammonia in the breath, the formation of white vapours on contact of the breath with a glass rod dipped in hydrochloric acid, frequently fails in cases with the most marked symptoms of uræmia. We must, therefore, expect further proofs, analyses of the blood and the excretions, before we can give that extension to toxæmia as a cause of various severe affections, which by various authors has been attributed to it. It is the same with putrid or septic fevers, under those conditions in which the blood is said to be in a state of dissolution. For all we know, ammonia may be a product of these pathological processes; and then we might expect to find it, in part at least, in the urine." (*Op. cit.*, pp. 224, 225.)

The opinion of M. Claude Bernard, in his late work (*Leçons sur les Propriétés Physiologiques et les Alterations Pathologiques des Liquides de l'Organisme*, Paris, Baillière, 1859), is adverse to admitting that carbonate of ammonia is capable of producing toxæmia. We have referred to this opinion more at length in another place. (See Appendix, Note A.)

The small quantity of ammonia entering into the composition of the normal urine, is, of itself, an element which rather tends to preclude the idea of its accumulating in the blood—in cases of retention of the urinary ingredients—in such quantities as to prove noxious, even if we consider it to be a toxic agent. At all events, under such a supposition, it would require a considerable time for bad effects to arise. And even granting all these conditions, the phenomena springing from retention of the other more abundant constituents would preponderate; unless, by that sort of "elective affinity" previously spoken of, ammonia alone were seized upon and retained in the circulation—the other matters being eliminated and excreted.

Again, it is by no means impossible, although not definitely proved, that ammonia may be essential to the integrity of the blood; in which case, any pathological inferences from its presence, unless occurring in very large and improbable quantities, could hardly be drawn. And especially in view of the fact that the nature of that ferment supposed by Frerichs to be necessary for the production of carbonate of ammonia from urea contained in the blood, is yet unknown, must doubt envelop the whole question, pathologically, until further experiments shall be made, and its existence and real character be ascertained, or its nonentity determined.

In respect to the question as to the necessity of ammonia to the proper constitution and healthy condition of the blood, Dr. Thudichum has some remarks which, under cover of a little pleasant facetiousness, contain

Speaking of the elimination of ammonia—ingested into the system in an unchanged state—by the kidneys, he says:—

> "It remains to be seen whether caustic ammonia and carbonate of ammonia are eliminated in a similar manner. It remains, also, to be ascertained whether the organism produces any ammonia under ordinary circumstances, or whether the ammonia in the urine is simply introduced by our food and drink, or by the air which we breathe. Some articles of food are rich in ammonia, *e. g.*, radishes. The smoke of tobacco contains a large share of ammonia; and any person remaining for any length of time in a room filled with this ambrosial offering to Apollo, must inhale such quantities of ammonia as must materially increase the ordinary amount in his urine. If ammonia be really essential to the blood, the anti-tobacco leaguers may yet hear the argument advanced, that tobacco-smoking is really essential to keep our fibrine in solution, and that smoking has of late become so much more common because the ordinary sources of this 'food,' the cesspools, dunghills, and other like accompaniments of human and animal habitations, have been done away with. A still greater amount of ammonia is of necessity inhaled where both the sources just mentioned flow without restraint." (*Op. cit.*, p. 224.)

The fibrine in the blood of a very considerable proportion of the population of America ought to be in a good state of "solution" if the smoking of tobacco be in any degree conducive thereto! Let us hope that such is the effect of "the weed," *viâ* combustion and inhalation!

Several observers have stated the very small amount of ammonia which can be ascertained to exist in healthy urine.[1] Simon (*Chemistry*, Syd. Soc. edit., vol. ii. p. 132) says it "cannot be very easily demonstrated in healthy urine." Liebig (*Lancet*, 1844), referred to by Dr. Day, Editor of *Simon's Chemistry* (*loc. cit.*), pronounced the presence of ready formed ammonia in the urine, as only indicated by "very minute or doubtful traces;" and stated also that "these traces probably pre-existed in the food partaken of." Dr. Day subsequently remarks: "Experiments for the determination of the amount of ammonia in the urine of healthy individuals may become of importance in judging of pathological states; for in fevers and other diseases, the amount of ammonia in the urine increases considerably. It is possible that by analyzing the urine we may, in the increasing or decreasing amount of ammonia, obtain a measure for the alterations which take place in diseases."

As has been previously remarked, there seems not to be a sufficient amount of evidence from which to educe satisfactory conclusions relative to any pathological influence ammonia may have upon the system when present therein in unusual quantity. Those who attach such a distinct power to it in the production of uræmic intoxication and eclampsia, have yet to procure and offer much additional evidence, before their doctrines can be unhesitatingly and fully accepted. The preliminary structure certainly has a fair and plausible appearance, but needs full development and confirmation. We have endeavoured to present whatever is available and reliable upon the present topic, so far as our means of information permit.

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[1] "Ammonia exists only in the urine in combination with the muriatic, phosphoric, and lithic acids." (Prout, *op. cit.*, p. 555.)

The examination of the relations of ammonia to the urine and the blood concludes the plan originally proposed by us in discussing the subject under consideration. It occurs to us, however, that a few words may appropriately be added relative to the *iron* and the *colouring matter* of the urine—*uræmatine.* These we will briefly notice under one head.

IRON AND URÆMATINE.[1]

Iron and uræmatine exist normally together in combination[2] in the urine. Of course, variable amounts of iron must be found at different times in the system, according to the nature and amount of the ingesta; and as the mineral in some of its various medicinal forms is very extensively used, there must be in many persons a large quantity introduced into the circulation.[3] We know the marked beneficial effect of this medication in a large class of cases, especially in those of an anæmic and chlorotic character, and its employment was doubtless owing, first and mainly, to the knowledge of the fact that iron is a normal constituent of the blood. That portion of the vital fluid of which it is an integral part, is, as is well known, the *hæmatine* or red colouring matter. Chemists have been inclined to believe uræmatine "a derivate" of hæmatine, so great is its resemblance to it. (Thudichum *et al.*)

But little that is positive can be said upon this subject, as to any pathological deductions. We can hardly conceive of a sufficient quantity of iron being accumulated and retained in the blood—*if derived merely from the amounts contained in the urine*—to prove injurious. It is not infrequently observed in practice, that only certain quantities of iron can be medicinally ingested, without giving rise to headache, fulness and turgidity of the bloodvessels, with other disagreeable symptoms, principally of a plethoric also, are far more easily affected by chalybeates than others. In some, this amounts to a species of idiosyncrasy which precludes the use of such remedies, unless combined with other articles whose employment is often not desirable, and sometimes is inadmissible, for peculiar and varying reasons. Thus, we know persons whom iron, given in any considerable quantity, will *purge* persistently; and in some such instances, if opium be combined with it for the purpose of restraining the action of the bowels, *nausea* takes the place of the diarrhœa—a species of intolerance of the medicament seems to exist. This is doubtless not uncommon. There are other manifestations sufficiently indicative of the powerful action of iron upon the system. But such phenomena, and those more especially mentioned above, are distinctly referable to considerable quantities of iron thrown into the organism at once, or gradually. As we have intimated, there appear to be no sufficient *data* whereupon to found any conclusions in reference to a possible pathological result of retention in the blood *of the iron derived from the urine.*[1]

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[1] *Iron:* Symbol; Fe. Equivalent; 28.0.
Uræmatine: Elementary composition unknown.
Thudichum.

[2] Harley; cited by Thudichum.

[3] Notwithstanding that iron is frequently thus largely ingested, it is a curious and hitherto unexplained fact, that it is not found in the liquid excreta. Its mode of elimination is therefore unknown. Upon this point, M. Cl. Bernard remarks: "Iron is the only substance which exists normally in the blood, which has not been found in the excreted liquids. How is it eliminated? This is undecided. A small quantity only is absorbed even in medicamentary usage. It has been found in the hair; but this is a very slow method of elimination." (*Leçons sur les Propriétés Physiologiques et les Alterations Pathologiques des Liquides de l'Organisme,* Paris, Baillière, 1859, vol. i. pp. 448–9.)

With regard to the curative properties of iron in certain affections, the statements of Dr. Golding Bird have a peculiar fitness to our subject. He says:—

> "Among the remedies which appear most successful when food is not converted into healthy chyle, and an unhealthy state of the blood from the presence of imperfectly assimilated matters results, the preparations of iron deserve notice. I have repeatedly seen copious deposits of uric acid, in persons of low power, completely disappear *pari passu* with the cure of the pseudo-chlorotic symptoms present, by the use of this important drug."

This is literally "killing two birds with one stone," enriching the blood, and depurating it, also. There can be little to fear from *iron* when judiciously administered; it is to be hoped that any "morbid effects" from large amounts existing in the circulation, in whatever way this may be produced, will by and by be satisfactorily and fully ascertained and explained. It would seem, however, that, had any very marked pathological phenomena been constantly, or even frequently, specially dependent upon accumulation from urinary obstruction or failure of due elimination, the acumen of the numerous competent observers of disease, so continually on the watch for such manifestations, would, ere this, have given us some positive ideas upon the subject.

Uræmatine.—There are some interesting observations relative to *uræmatine,* which it seems desirable to present at this time. Uræmatine is believed to be derived, in great measure, from the hæmatine set free during the disintegration of the blood-corpuscles, which is always taking place. *Cholæmatine*, the colouring matter of the bile, is also considered a product of hæmatine. The colour of hæmatine is known to be very persistent. The colour of the fæces and urine is ascribed by Dr. Thudichum to "effete hæmatine." He also alludes to the fact that iron is always conjoined with uræmatine as a component element, and considers this as confirmatory of its origin from the colouring matter of the blood-corpuscles.[1]

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[1] "The analysis of the urine may prove useful for determining the amount of iron which enters the blood and circulation when it is taken as a medicine." (Thudichum.)

Vogel has shown that the amount of uræmatine is increased in acute febrile diseases; in those which partake of an anæmic or chlorotic nature there is less colouring matter discharged. This is ascribed to the diminution of the disintegration process constantly going on, as has been said, with greater or less activity. In typhoidal conditions, and in fevers of a septical type, there being great dissolution of the blood, the colour of the urine is heightened.

When hæmato-globuline appears in the urine, it is indicative of destruction of the blood-corpuscles, and is a sign of serious import. If only transitory, however, and not recurrent, the case becomes more hopeful. "But when it is a symptom of severe scorbutic or septic disorders, it is a sign of great danger to the life of the patient. Suppression of the urine, and discoloration of the skin, when following the discharge of urine rich in hæmatoglobuline, are also very unfavourable, and are forerunners of a fatal termination of the case." (Thudichum, *op. cit.*, p. 237.)

In discussing a question like that proposed for the subject of this essay, there is much to trammel us, on the score of incomplete revelations of the chemical and pathological elements concerned. The great interest and importance of the theme itself, and of the studies and investigations rendered necessary for its thorough and progressive examination, will more and more rapidly bring hidden truths to light. Practical experiments, and the continued observation of those engaged in medical pursuits, were never more needed than in elaborating the processes and extending the records already so well begun—instituting new methods and employing more profound scrutiny. And especially to those who have the great advantage of being connected with large hospitals, are rare opportunities afforded for these pursuits, destined, as they certainly are, to benefit suffering humanity, by enabling the members of our profession with more facility and certainty, in this class of cases, *prius cognoscere, dein sanare.*

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[1] For methods of ascertaining the quantity of uræmatine in healthy urine, the amount passed in twenty-four hours, and much valuable information relative to the various shades of colour observed in urine, together with illustrations, see Dr. Thudichum's work. Consult, also, Vogel, "Archiv. des Vereins für gemeinschaftliche Arbeiten," Bd. i. p. 137, 1853.

APPENDIX.

NOTE A.

Urea; questions relative to its agency in the system.

In a lately published work,[1] M. Claude Bernard discusses the question whether urea is to be considered a toxæmic agent, either *per se* or by any product derived from it. The respect which the opinions of this distinguished observer must always command, and the very recent date of the conclusions at which he has arrived upon this subject, induce us to present such of them as are most essential to our purpose.

"Is urea a poison?" asks M. Bernard, referring to the views of Frerichs. A poisonous substance, he goes on to say, although it may, like urea, be present in the circulation, is not necessarily toxic in every, even the smallest amount. "A violent poison may, then, exist in the blood, in very noticeable proportion, without occasioning symptoms of poisoning, if elimination be sufficiently rapid; we are not, consequently, authorized to declare that urea is not a poison because it is formed in the blood in considerable quantities." (Vol. ii. p. 33.) Bernard then refers to the experiments of M. Gallois, who found the injection of urea into the blood, innocuous, even in large quantities. We must, then, he continues, admitting the fact of innocuousness, seek another explanation. The theory of Frerichs does not seem sufficient, according to Bernard, to account for the phenomena observed. If carbonate of ammonia be injected in small quantity into the vessels, there is no result; and even when introduced into the veins of animals in larger amounts, although an extreme agitation was produced, yet life was maintained. Carbonate of ammonia, moreover, has nearly always been found both in pathological and in healthy blood. "Consequently, its presence in the blood cannot explain the special accidents of uræmia." Bernard therefore adopts another explanation, and puts forward the following views in preference to the others referred to. 1. The condition of the kidneys in advanced renal disease; there is softening, breaking down of the tissue—"fonte putride." 2. By destroying the nerves going to the kidneys, their disorganization is produced; softening and purulent formations are brought on; pus is thrown into the circulation; and thus renal nutrition is wholly perverted, the kidneys becoming decomposed. In this state of things, Bernard is inclined to ascribe the poisoning of the blood and the resulting phenomena to the agency of the putrid matter thrown into the circulation from the injured kidney. He admits, however, that new experiments are necessary. Thus, we ought to see what effects will be produced by injecting the putrid matter from a kidney which has become disorganized by artificial destruction of its nerves, into the blood of a healthy animal—in fact we must ascertain whether the accidents supervening under such conditions will put on the aspect of the nervous phenomena of uræmia.

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[1] "Cours de Médecine du College de France. Leçons sur les Propriétés Physiologiques et les Alterations Pathologiques des Liquides de l'Organisme." Par M. Claude Bernard, Membre de l'Institut de France, Professeur de Médecine au College de France, Professeur de Physiologie Générale à la Faculté des Sciences, etc. etc. Paris, J. B. Baillière et Fils, 1859.

"There is no physiological office (*rôle*) known as especially appertaining to urea; it is a purely excrementitious substance, not a secretion. It is regularly eliminated by the kidneys; when this elimination is interfered with, we observe the supervention of grave phenomena, without being able to say whether they are, either primarily or secondarily, the consequence of an accumulation of urea in the blood, or whether they are dependent upon the lesion which has caused the accumulation." The phenomena referred to, says Bernard, have received the name *uræmia.* "Is it proper to class under the same category the convulsions of lying-in women?" [as we have seen has been done by Braun and others.] This is a question, according to Bernard, which is yet to be examined, and which it would be premature to pretend positively to answer at present. *En resumé*, Bernard thinks the accumulation of urea, or of carbonate of ammonia, in the blood, cannot explain the disorders alluded to; but that it is far more plausible to believe them referable to destruction or injury of the renal nerves.[1] [This, however, would not explain the so-called uræmic convulsions of pregnancy, since a sort of artificial, or curable, Bright's disease—curable by the act of parturition—may then exist. The question is yet in dispute.]

Dr. E. Brown-Séquard, in the number of the *Journal de la Physiologie de l'Homme et des Animaux*, for January, 1859, makes the following comments upon Dr. Hammond's experiments and conclusions; and we are happy to avail ourselves of this distinguished physiologist's opinions upon this subject, especially in view of the very recent date of their announcement. Dr. Séquard, after giving Dr. Hammond's views and processes, as published in *The North American Medico-Chirurgical Review* for March, 1858, goes on to say: "We shall confine ourselves to the following remarks: 1. The author has not shown so conclusively, as he seems to suppose, the non-conversion of urea into ammonia (he employed hydrochloric acid as a reagent); 2. Injection into the jugular vein, of substances whose action is sought for, is a procedure very liable to make us suppose a non-poisonous substance poisonous, by reason of the disturbance which the injection of any liquid whatever into this vein sometimes produces in the movements of the heart; 3. In dogs from whom the kidneys have been removed, the injection of four ounces of pure water is capable of producing the same morbid effects which the author observed after injecting the different salts and urea, contained in four ounces of water. We conclude, then, that Dr. Hammond's experiments, exceedingly interesting though they are, are not sufficient to overthrow the ingenious theory of M. Frerichs. Of the two divisions of this theory, that which considers urea not to be a poison, or, at least, not to be capable of producing uræmia, seems scarcely to be shaken by the experiments of Dr. Hammond. As to the other division, according to which uræmia is a poisoning due to the carbonate of ammonia, more powerful arguments than those we have cited above have already been urged against it, and, at the present pendent upon various causes, among which, poisoning by carbonate of ammonia has only a variable proportion of influence.

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[1] For Bernard's remarks, *in extenso*, see the work cited, vol. ii. pages 34—37 inclusive.

"The experiments of M. Gallois (*Thèse inaugurale*, Paris, 1859) may be considered more positive than those of the American physiologist, in showing that urea is a poison. M. Gallois has seen rabbits die, after violent convulsions, from the administration of twenty grammes of urea, introduced into the stomach. But we have no proof that urea is not transformed into carbonate of ammonia, or into some other toxic element." (*Loc. cit.*)

M. Guérard (*Dict. de Médecine*, in 30 vols., Art. *Sang*), referring to the accumulation of urea in the blood, thus writes: "This accumulation in the blood of a principle whose elements are endowed with such an excessive mobility, and which separate themselves with the greatest facility in order to transform themselves into carbonate of ammonia, eminently deserves to arrest the attention of physiologists, on account of the accidents to which it will unfailingly give rise." He then asks, "if it be not probable that the ammoniacal odour pervading the excretions of those who have long had suppression of urine, is the result of the metamorphosis mentioned? The plausibility of this opinion becomes greater if it be remembered that many observers have assured themselves of the existence of urea in the fluids effused into the various serous cavities, in persons who have died of Bright's disease." M. Guérard refers, in this connection, to Dr. Babington. (*Cyclopædia of Anatomy and Physiology*, Art. *Blood.*)

NOTE B.

The Relation of Uric Acid to Gout.

Dr. Barlow (*A Manual of the Practice of Medicine*, London, 1856), referring to the explanation given by Dr. W. Budd (*Medico-Chirurgical Transactions*), in respect to the elective affinity manifested by certain morbific matters for certain organs and parts of the body, speaks of the support which the humoral pathology of the various gouty affections may reasonably derive from these views; but he is by no means inclined to allow uric acid the important position of chief agent in the production of gout. He says: "It is not, however, intended to imply by what has been said, that lithic or uric acid is the alone or efficient cause of gout; for if this were true, we should always have gout when uric acid is in abundance [not so, we would remark, if it be in process of elimination, and is not *retained* and *accumulated in the blood*—for such are the elements evidently required for the production of the disease], and never have gout without it; whereas, the presence of the one without the other, especially of uric acid without gout, is a matter of everyday experience." [For the reason above alleged; for if uric acid appear in abundance in the urine, we infer from the fact alone, as a rule, its free elimination; consequently, it does not accumulate in the blood, and gout does not occur.] Dr. Barlow continues: "Upon what the gouty diathesis or susceptibility depends we know nothing [?]; it manifests itself in the system by an affinity for the gouty poison (uric acid it may be) in different parts. If this diathesis be such as to produce an affinity of extraordinary intensity, there may be a local excess of this substance, without any such excess, or even with a deficiency, in the system at large, just as there may be a local hyperæmia, although the general state of the system may be anæmic. This explanation of the difficulty is merely suggested as possible, not enunciated as certain; it nevertheless derives confirmation from the recent observation of Dr. Garrod that uric acid is present in the serum, effused when a blister has been applied over a joint affected with gouty inflammation." (*Op. cit.*, English edition, 1856, p. 143.) Aside from the force of the evidence adduced by Dr. Garrod in the test referred to by Dr. Barlow, we cannot think the position of the latter author is strengthened by the analogy which he attempts to establish—or the similarity which he would imply, in vital action—between local hyperæmia in general anæmic states and the deposition of urate of soda by elective affinity. In fine, in the one case, the blood, although deteriorated, does not, in the circumstances proposed, contain a poison; whereas, in the latter case, it does, or the local manifestations thereof would not occur. Mere local hyperæmia, occurring as above mentioned, cannot be properly compared with the local exhibition, by vicarious action, of the product of an abnormal amount of uric acid in the blood.

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